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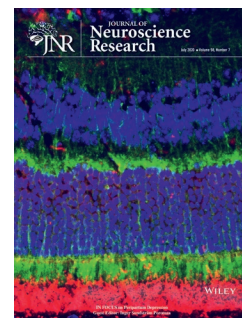
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REVIEW

Dysregulation of synaptic pruning as a possible link between intestinal microbiota dysbiosis and neuropsychiatric disorders



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Abstract

The prenatal and early postnatal stages represent a critical time window for human brain development. Interestingly, this window partly overlaps with the maturation of the intestinal flora (microbiota) that play a critical role in the bidirectional communication between the central and the enteric nervous systems (microbiota-gut-brain axis). The microbial composition has important influences on general health and the development of several organ systems, such as the gastrointestinal tract, the immune system, and also the brain. Clinical studies have shown that microbiota alterations are associated with a wide range of neuropsychiatric disorders including autism spectrum disorder, attention deficit hyperactivity disorder, schizophrenia, and bipolar disorder. In this review, we dissect the link between these neuropsychiatric disorders and the intestinal microbiota by focusing on their effect on synaptic pruning, a vital process in the maturation and establishing efficient functioning of the brain. We discuss in detail how synaptic pruning is dysregulated differently in the aforementioned neuropsychiatric disorders and how it can be influenced by dysbiosis and/or changes in the intestinal microbiota composition. We also review that the improvement in the intestinal microbiota composition by a change in diet, probiotics, prebiotics, or fecal microbiota transplantation may play a role in improving neuropsychiatric functioning, which can be at least partly explained via the optimization of synaptic pruning and neuronal connections. Altogether, the demonstration of the microbiota's influence on brain function via microglial-induced synaptic pruning addresses the possibility that the manipulation of microbiota-immune crosstalk represents a promising strategy for treating neuropsychiatric disorders.

KEYWORDS

glial cells, neural development, neurodegenerative diseases, neurodevelopmental disorders, oligodendrocytes

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1 | INTRODUCTION

At the most fundamental level, brain function is based mainly on computations performed by synapses. Perturbations in physiological synaptic structure and function and dysregulated synaptic formation, elimination and plasticity have been hypothesized to underlie altered neuronal function in complex neuropsychiatric disorders, such as autism spectrum disorder (ASD) and schizophrenia (SZ) (Wang, Christian, Song, & Ming, 2018). At the early stages of life, synapse formation (synaptogenesis) exceeds elimination, yielding excessive synapses essential for the assembly of neural networks (Bruer, 1999). Subsequently, synaptic elimination/pruning outpaces synaptogenesis, providing selection and maturation of synapses and neural circuits from childhood through adolescence (Tang et al., 2014). Different patterns of dysregulated synaptic pruning have been linked to various neuropsychiatric phenotypes, confirming the importance of the balanced synaptic formation and pruning in normal brain function. Recent studies have pointed to a key role for microglia, the innate immune cells of the central nervous system (CNS), in synaptic pruning by purging the brain of infrequently used synapses (Weinhard et al., 2018).

In mammals, microglial activation and function during developmentally sensitive periods can be modulated by the microbiota (Erny et al., 2015), the different resident phyla and bacterial species in the gastrointestinal (GI) system (Dickerson, Severance, & Yolken, 2017; Fond et al., 2015; Nemani, Hosseini Ghomi, McCormick, & Fan, 2015). Many causes can alter the well-being of the microbiota including administration of antibiotics or non-steroidal anti-inflammatory medicines, herbicides, ingredients present in food (sugar or gluten) or in water (chlorine) (Larroya-Garcia, Navas-Carrillo, & Orenes-Pinero, 2019). In turn, the imbalance in microbiota composition (dysbiosis) can affect the function of neuronal circuits *via* synaptic pruning alteration (Tognini, 2017). Indeed, the current data indicate that various neuropsychiatric disorders are associated with microbiota alterations (Cenit, Sanz, & Codoñer-Franch, 2017; Kim & Shin, 2018). Hence, a better understanding of the effect of intestinal microbiota dysbiosis on synaptic pruning can pave the way to enhance the treatment outcomes of neuropsychiatric disorders.

2 | SYNAPTOGENESIS AND SYNAPTIC PRUNING DURING BRAIN DEVELOPMENT

Synaptogenesis is a complex multifactorial developmental process which enables the formation of synapses between neurons. Synapse formation is essential for all nervous system functions including establishing neural circuits and ultimately expressing complex behavior (Hong & Park, 2016). Across mammalian species, neurons present at birth undergo a period of overproduction of their arborization and synaptic contacts to increase synaptic density (Semple, Blomgren, Gimlin, Ferriero, & Noble-Haeusslein, 2013). In humans, the thickness of the cortex typically increases in the first few years of life as a result of excessive synapse formation (Tau & Peterson, 2010), with

Significance

The association between the intestinal microbiota and brain function is not fully understood. In this review, we propose synaptic pruning dysregulation as a possible link between microbiota dysbiosis and neuropsychiatric disorders including autism, schizophrenia, bipolar and attention deficit hyperactivity disorders. To this end, the alleviation of neuropsychiatric symptoms *via* improving the intestinal microbiota composition might be partly explained by the modulation of microglial function, leading to a modification in neuronal connections. Therefore, the microglial activity and its effect on synaptic pruning may be good markers for testing the efficacy of probiotics and prebiotics as supportive therapeutic approaches for neuropsychiatric disorders.

different cortical regions showing their peaks of synapse formation periods (Huttenlocher & Dabholkar, 1997). For example, synaptic density in the primary visual cortex reaches its peak between the ages of 4 and 12 months (Tau & Peterson, 2010). Synaptogenesis in the prefrontal cortex that requires remodeling to achieve fully mature and complex behavior begins about the same time as in the visual cortex, but it continues to reach its peak through the second and third year of life (Huttenlocher, de Courten, Garey, & Van der Loos, 1982; Huttenlocher & Dabholkar, 1997; Kostović, Judaš, Petanjek, & Šimić, 1995; Lenroot & Giedd, 2006).

Later in life, at the time of early adolescence, cortical thickness decreases by pruning weak and redundant synaptic connections, and strengthening the remaining synapses (Sowell, Thompson, & Toga, 2004; Wang et al., 2018). Synaptic pruning is a crucial process to enhance neuronal transmission and to establish the finely tuned circuitry by eliminating ineffective synapses and strengthening the vital neuronal connections, which allows for more efficient processing of adult cognition. In mammals, axonal and dendritic processes constitute approximately 60% of cortical volume (Tau & Peterson, 2010), and pruning of these processes may represent the source of cortical thinning (Paus, Keshavan, & Giedd, 2008).

Synaptic pruning begins in late gestation and becomes increasingly active postnatally (Tau & Peterson, 2010). The time course for pruning differs across brain regions, with sensory and motor cortices undergoing dramatic fine-tuning after birth, followed by association cortices and the corpus callosum, and later by regions that subserve higher cognitive functions (Levitt, 2003). In early childhood (2 and 7 years of age), neuronal density in layer III of the prefrontal cortex decreases from 55% to approximately 10% above adult levels (Huttenlocher, 1979). During later childhood (7–15 years of age), synaptic density in the frontal cortex decreases by approximately 40% (Lidow, Goldman-Rakic, Gallager, & Rakic, 1991). These synaptic changes occur in the absence of any significant neuronal loss and are accompanied by a reduction in the expression of genes involved in axonal and synaptic functions (Colantuoni et al., 2011). The continuous cortical thinning *via* synaptic pruning throughout

late childhood and adolescence reflects ongoing maturation of neural networks which underlies behavioral changes at these periods (Semple et al., 2013).

3 | DYSREGULATED SYNAPTIC PRUNING IN NEUROPSYCHIATRIC DISORDERS

Disturbed synaptic pruning has been linked to deficits in neuronal circuitry with behavioral impairments as a consequence. Over the last decade, mutations in several genes that encode the required proteins for synapse formation, development, plasticity, and pruning were linked to the psychopathology of multiple complex neuropsychiatric disorders including ASD, SZ, attention deficit hyperactivity disorder (ADHD) and bipolar disorder (BD) (Wang et al., 2018; Zoghbi & Bear, 2012). This supports the hypothesis that neuropsychiatric disorders are, in part, the consequences of a developmental synaptopathy. Interestingly, a survey of over 9,000 people representative of the US population in the period between February 2001 and April 2003 has indicated that the peak age of onset for having any mental health disorder is 14 years (Kessler et al., 2005). Moreover, among adult cases with neuropsychiatric disorders, 73.9% have developed

behavioral symptoms and received a diagnosis before 18 years of age and 50% before 15 years of age which concurrent with the peak of the synaptic pruning process (Kim-Cohen et al., 2003).

Different patterns of dysregulated synaptic pruning are associated with various neuropsychiatric phenotypes, with grey matter loss in the bilateral anterior- and subgenual cingulate cortex in schizoaffective disorder and BD, whereas general grey matter loss was observed for SZ (Gogtay, 2008; Mattai et al., 2011). In contrast, acceleration in brain growth of all regions except occipital grey matter in the early years of patients with ASD was observed (Schumann et al., 2010).

3.1 | Autism spectrum disorder

ASD is a complex neurodevelopmental disorder with a strong genetic component, which refers to a constellation of clinical conditions with two main phenotypic characteristics: impairment in social communication and patterns of repetitive restrictive behavior (Berkel et al., 2018). Remarkably, the time when ASD symptoms appear or become more apparent, at around 2–3 years old, coincides with the window for the initial generalized synaptic pruning event (Figure 1).

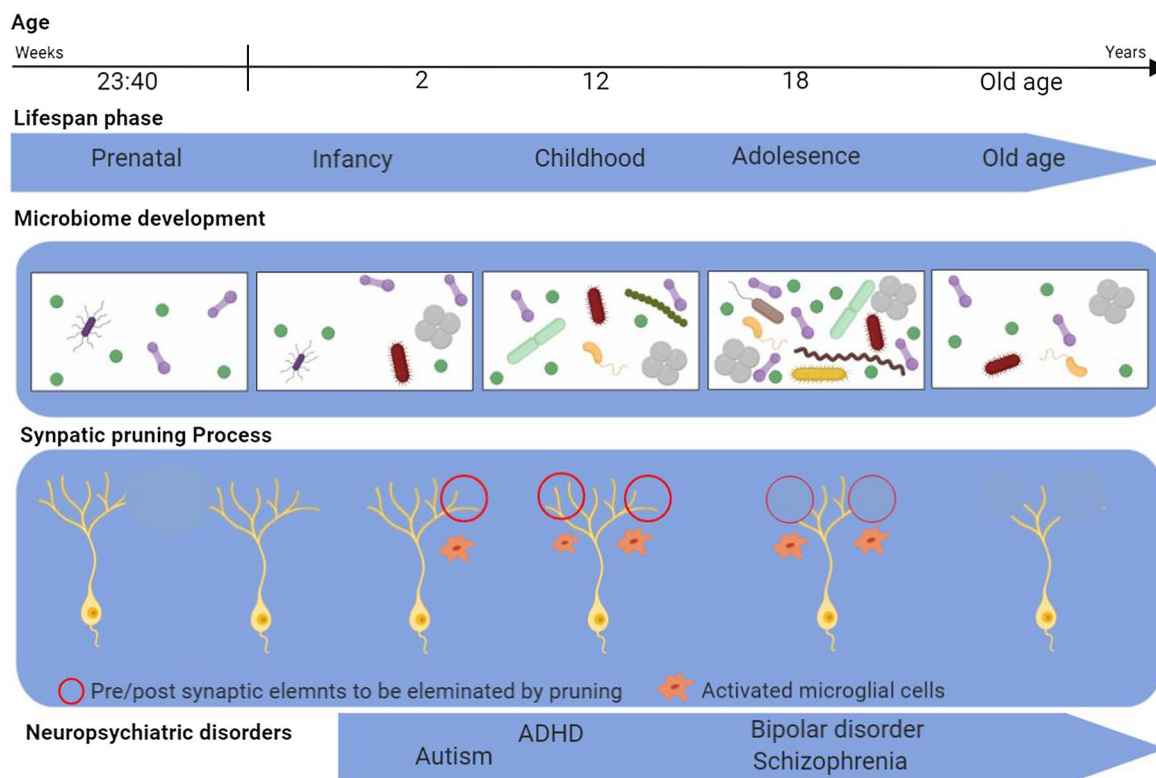


FIGURE 1 The onset of neuropsychiatric disorders symptoms in relation to synaptic pruning and microbiota development in the intestine. Autism spectrum disorder and attention deficit hyperactivity disorder symptoms appear concurrent with the start of the synaptic pruning process. In contrast, schizophrenia and bipolar disorder symptoms are parallel with the end of the synaptic pruning process. The microbiota composition is continuously changed throughout the lifespan with major changes concurrent with the synaptic pruning process. The association of microbiota alteration to neuropsychiatric disorders via synaptic pruning is an important example of the signaling between the central and the enteric nervous systems (microbiota-gut-brain axis) [Color figure can be viewed at wileyonlinelibrary.com]

Some children diagnosed with ASD feature a significant excess in brain size and weight in the first year of life due to a high acceleration rate of brain growth (Courchesne, Carper, & Akshoomoff, 2003). This involves an enlargement in different brain regions with an expansion in both grey and white matter volume as observed by magnetic resonance imaging (MRI) studies (Courchesne et al., 2003; Gaffney, Kuperman, Tsai, & Minchin, 1989; Hardan, Muddasani, Vemulapalli, Keshavan, & Minshew, 2006; Piven et al., 1992, 1995). Moreover, diffusion tensor images from the brains of ASD children have shown an increase in axons and myelination between neighboring areas of the brain compared with more distal connections, suggesting an increase in connectivity (Walker et al., 2012). On the microstructural scale, synaptic densities of pyramidal neurons in the temporal lobe are observed in postmortem studies to be increased in the brains of children and adults with ASD (Hutsler & Zhang, 2010; Tang et al., 2014). Moreover, the reduction in cortical spine density that is observed in brains of typically developing adolescents is diminished in individuals with ASD (Tang et al., 2014), suggesting a deficit in pruning, at least at this later age. Besides, mice carrying rare, penetrant mutations that are found in individuals with ASD show elevated spine densities in the temporal cortex and cerebellum (Kim et al., 2017; Piochon et al., 2014; Tang et al., 2014) and deficient adolescent pruning (Tang et al., 2014). Altogether, children with ASD are believed to have excess synapses and synaptic connections in the brain due to deficits in synaptic pruning during early brain development (Tang et al., 2014), which may account for the abnormal patterns of brain connectivity in ASD (Belmonte et al., 2004).

The idea that enhanced connectivity may have disadvantageous effects on brain function and cognition was supported by mouse models. Mice with excessive synaptic connections due to a failure in synaptic pruning were primarily able to learn spatial locations but unable to re-learn new locations (Afroz, Parato, Shen, & Smith, 2016). This indicates that too many brain connections may put limitations on the learning potential. Moreover, by impairing synaptic pruning in mice, they exhibited ASD-like phenotypes including social interaction deficits and repetitive behavior (Fernandez de Cossio, Guzman, van der Veldt, & Luheshi, 2017; Kim et al., 2017). A similar process to the methodology in the aforementioned mouse studies is suggested to play a role in the impairment of synaptic pruning in humans diagnosed with ASD. Therefore, there is evidence from mouse studies to support the claim that children diagnosed with ASD are believed to have increased synaptic connections in the brain due to deficits in synaptic pruning during early brain development (Tang et al., 2014). However, caution should be taken when translating mice finding to humans. Although a large variety of mouse behavioral tests are currently used and showed considerable face validity in testing the ASD core symptoms, the lack of a "human-specific" read-out resulting from complex gene-environment interactions occurring during early postnatal stages and adolescence is the main limitation (Pasciuto et al., 2015). Therefore, the validity of drawing solid conclusions from mice to humans is still limited.

3.2 | Attention deficit hyperactivity disorder

ADHD is a complex brain disorder marked by an ongoing pattern of inattention, hyperactivity, and impulsivity that significantly impacts many aspects of behavior as well as cognitive performance (Singh, Yeh, Verma, & Das, 2015). Structural MRI studies on people with ADHD have revealed a subtle but significant grey and white matter loss (Rapoport et al., 2001), which was not progressive (Castellanos et al., 2002). Moreover, cross-sectional MRI studies have shown a reduction in the size of cortico-striatal brain regions that are known to develop late in adolescence (Berger, Slobodin, Aboud, Melamed, & Cassuto, 2013; Krain & Castellanos, 2006), in the volumes of the right and left inferior-posterior cerebellar lobes (Mackie et al., 2007), and in the thickness of cerebellar brain region (Shaw et al., 2007). However, the structural development of almost all cortical regions in ADHD children was similar to non-psychiatric control subjects (Shaw et al., 2007). To this end, it is suggested that ADHD children suffer from a maturational delay due to a lag in synaptic pruning (Rubia, 2007; Shaw et al., 2007; Vaidya, 2012), which is supported by the fact that 80% of children grow out of ADHD in adulthood (Faraone et al., 2000). The cortical maturation delay in ADHD was most prominent in the lateral prefrontal cortex, which supports the ability to suppress inappropriate responses and thoughts, executive control of attention, evaluation of reward contingencies, and working memory (Shaw et al., 2006, 2007). In contrast, only the motor cortex had a maturation peak 4 months ahead in children diagnosed with ADHD compared to control children, which may account for the impulsivity in people with ADHD (Shaw et al., 2007).

3.3 | Schizophrenia

SZ is a complex, mental disorder characterized by an array of symptoms including delusions, hallucinations, disorganized speech or behavior, lack of motivation, and impaired cognitive ability (Patel, Cherian, Gohil, & Atkinson, 2014). Unlike ASD, the onset of the symptoms of SZ typically occurs between the ages of 15 and 25 and coincides with later stages of synaptic pruning in the adolescent prefrontal cortex (Selemon & Zecevic, 2015).

The association between synaptic pruning dysregulation in adolescence and SZ was first hypothesized by Feinberg in 1982 (Feinberg, 1982). This hypothesis was revisited in 1994 by analyzing postmortem brains which showed that excessive synaptic pruning in the excitatory glutamatergic neurons in the prefrontal cortico-cortical and -sub-cortical areas was seen in SZ neuropathology (Keshavan, Anderson, & Pettegrew, 1994). Synaptic pruning ends at the age of onset for SZ (Wang et al., 2018; Figure 1), which further links the dysregulation of synaptic pruning to the SZ pathophysiology. In one study, the grey matter volume, as a measure of the extent of synaptic pruning (Sowell, Thompson, Tessner, & Toga, 2001), was reduced in both males and females diagnosed with SZ and correlated with reduced cognitive performance (Gur, Turetsky, Bilker, & Gur, 1999). This finding was replicated

in another study which showed a fourfold excess of permanent grey matter loss in SZ compared to control subjects evaluated prospectively over 5 years (Thompson et al., 2001). A meta-analysis study including over 18,000 subjects revealed that intracranial and total brain volume in patients with SZ was significantly decreased (Hajima et al., 2013). Patients with SZ revealed a specifically reduced grey matter volume in the prefrontal cortex (Zhang et al., 2016), which may account for their disturbed behavioral inhibition.

Neuropathologic studies indicated that the grey matter reduction in the brains of individuals with SZ is due to cortical thinning, with the greatest severity in the frontal lobes due to primarily shrinkage in neuropil combined with a decrease in neuronal size (Andreasen et al., 2011; Berdenis van Berlekom et al., 2019; Osimo, Beck, Reis Marques, & Howes, 2019). Moreover, the locus of complement factor C4A that, among other functions, regulates synaptic pruning is one of the genetic loci significantly associated with SZ (Sekar et al., 2016). C4A has also been shown to be expressed during the postnatal neurodevelopmental stage in proportion to the allelic risk association with SZ (Sekar et al., 2016). One of the functions of activated complement is the opsonization of synapses to facilitate phagocytosis by microglia, hence leading to enhanced pruning. In addition, neuroimaging studies confirmed the enhanced synaptic pruning in individuals with clinical high risk for developing SZ (Cannon et al., 2015). Based on the aforementioned studies, individuals with SZ are suggested to have fewer synapses due to excessive synaptic pruning and suboptimal fine-tuning of neural circuits mediating motor, sensory and cognitive functions (Berdenis van Berlekom et al., 2019; Forsyth & Lewis, 2017; Mallya & Deutch, 2018; Sellgren et al., 2019).

3.4 | Bipolar disorder

BD is a chronic mental health condition that is characterized by depressive and (hypo)manic mood episodes, as well as an impairment in cognitive ability (Gondalia, Parkinson, Stough, & Scholey, 2019). In BD, serial MRI scanning of adolescent patients has shown significant grey matter reduction in some areas of the brain including the bilateral anterior and subgenual cingulate cortex (Gogtay et al., 2007). In 2012, another study has shown that individuals diagnosed with BD suffer from a disruption of the emotional control networks during development linked with synaptic pruning dysfunction, which leads to abnormal ventral prefrontal-limbic modulation causing the onset of mania (Strakowski et al., 2012). In addition, the age of onset of BD and the monoaminergic synaptic density measured with PET measures were found to be interrelated (Zubieta et al., 1998).

4 | THE INFLUENCE OF MICROGLIA ACTIVATION ON SYNAPTIC PRUNING AND NEURONAL FUNCTION

Microglia are the innate immune cells of the CNS that account for 10%–15% of all cells found within the brain (Lawson, Perry, &

Gordon, 1992). Several studies have identified a set of critical signaling pathways between microglia and neurons (for a review, see [Neniskyte & Gross, 2017]). Importantly, microglia have been shown to play a major role in the synaptic pruning process by purging the brain of infrequently used synapses (Boksa, 2012; Paolicelli et al., 2011; Schafer & Stevens, 2013; Stephan, Barres, & Stevens, 2012; Trapp et al., 2007). The first indication that microglia are involved in synaptic pruning was demonstrated by a study that showed that the large-scale axonal remodeling in embryonic and early postnatal development in cats was accompanied by a phagocytic activity of microglia and astrocytes, which were suggested to contribute to axon elimination (Berbel & Innocenti, 1988). Other studies in diverse model systems and circuits, ranging from peripheral synapses in the neuromuscular junctions to central synapses in the cortex, hippocampus, thalamus, and cerebellum strengthened the role of microglia in synaptic fine-tuning (Darabid, Perez-Gonzalez, & Robitaille, 2014; Hoshiko, Arnoux, Avignone, Yamamoto, & Audinat, 2012; Ichikawa et al., 2011; Paolicelli et al., 2011; Sasaki et al., 2014a, 2014b; Schafer et al., 2012; Zhan et al., 2014).

Given the evidence presented above, it may be unsurprising that the dysregulation of microglial activity, particularly over-activation, has been linked to several neuropsychiatric disorders including SZ (Bloomfield et al., 2016; De Picker, Morrens, Chance, & Boche, 2017; Doorduyn et al., 2009; Marques et al., 2018; van Kesteren et al., 2017) and BD (Haarman et al., 2014). Excessive synaptic pruning mediated by microglia in SZ is further supported by genetic studies (Calabrò, Drago, Sidoti, Serretti, & Crisafulli, 2015; Cocchi, Drago, & Serretti, 2016). Genetic variants that are significantly associated with SZ include those in genes related to microglial activation pathways that contribute to synaptic pruning in the cortex and thalamus (Neniskyte & Gross, 2017). Reducing microglial activity *via* anti-inflammatory agents was able to enhance the antipsychotic effect for treating negative and cognitive symptoms of SZ (De Picker et al., 2017; Kato et al., 2011; Kroken, Sommer, Steen, Dieset, & Johnsen, 2019; Levkovitz et al., 2010) and to relieve depressive and manic symptoms in BD (Edberg et al., 2018; Mousavi et al., 2017; Savitz et al., 2018). Moreover, *in vitro* studies of antipsychotic agents—perospirone, ziprasidone, and quetiapine—as well as lithium showed attenuation of microglial activation (Bian et al., 2008; Fabrizi et al., 2017).

Many factors including genetic predisposition, head trauma, and infection can cause microglial overactivation, hence affecting the normal brain function by influencing synaptic plasticity and synaptic elimination (Boulanger, 2009; Goshen et al., 2007; Khairova, Machado-Vieira, Du, & Manji, 2009; Lui et al., 2016; Murray & Lynch, 1998). One genetic predisposition is for the complement factor C4A gene which had a strong risk association with SZ. The phenotype of C4A shows increased synapse engulfment and thus excessive synaptic pruning (Sellgren et al., 2019; Wang, Zhang, & Gage, 2019), and the “omic” studies revealed a link between C4A and SZ pathogenesis (Birnbbaum & Weinberger, 2019; van Mierlo, Schot, Bok, & de Witte, 2019). A recent meta-analysis on postmortem brain studies for the immune involvement in the pathogenesis of SZ showed a significant increase in

TABLE 1 Clinical studies on intestinal microbiota dysbiosis in patients with autism spectrum disorder, attention deficit hyperactivity disorder, schizophrenia, or bipolar disorder

References	Sample size	Mean age in years ± SD (Range)	Gender (Male/Female)	Changes in taxonomic composition (in PT compared to NC)	Association with clinical features (in PT compared to NC)	Limitations/Notes
Wang, Zhou, et al. (2019)	<ul style="list-style-type: none">ASD: 43; 19 with GI involvement24 without GI involvementNC: 31	<ul style="list-style-type: none">With GI problems: 4.2 ± 1.5 (2–8)Without GI problems: 4.5 ± 1.8 (2–8)TDS 3.5 ± 1.6 (2–6)	<ul style="list-style-type: none">With GI problems: (16/3)Without GI problems: (20/4)TDS (18/13)	<ul style="list-style-type: none">Five microbiome epitopes (MEs) were significantly ↑ (Four were very similar to peptides from human gap junction alpha-1 (GJA1), β-myosin heavy chain (MYH7), paired box protein Pax-3 (PAX3), and eyes absent homolog 1 isoform 4 (EYA1). One ME from Listeriolysin O protein, derived from the pathogenic microorganism <i>Listeria monocytogenes</i>, was also significantly ↑)Among the 29 MEs significantly ↓ in ASD PTs, 11 MEs were predicted peptides from pathogenic microorganisms such as <i>T. gondii</i> and <i>herpes simplex virus</i>	<ul style="list-style-type: none">ASD PTs have ↑GI problemsASD PTs with GI problems showed ↑ diversityASD PTs with/without GI involvement could be distinguished by the composition and/or abundance of MEsNo significant differences in stool IgA levels between ASD PTs with GI problems and ASD PTs without GI problems	<ul style="list-style-type: none">MEs have not been validatedSome clinical indicators were not collected in TD children
Zhai et al. (2019)	<ul style="list-style-type: none">ASD: 78NC: 58	<ul style="list-style-type: none">ASD: 4.96 ± 1.01NC: 4.90 ± 0.97	<ul style="list-style-type: none">ASD: (56/22)NC: (31/27)	<ul style="list-style-type: none">Significant higher taxa richness and diversity of gut microbiota in the ASD group compared to the NCThe microbiome of the ASD children was characterized by a significant increase in nine genera: <i>Bacteroides</i>, <i>Parabacteroides</i>, <i>Sutterella</i>, <i>Lachnospira</i>, <i>Bacillus</i>, <i>Bilophila</i>, <i>Lactococcus</i>, <i>Lachnobacterium</i>, and <i>Oscillospira</i>	<ul style="list-style-type: none">Carbon fixation pathways in prokaryotes and the citrate cycle were positively associated with <i>Bacteroides</i>, <i>Oscillospira</i>, and <i>Sutterella</i>. Ether lipid metabolism and sporulation were negatively related to <i>Parabacteroides</i>	<ul style="list-style-type: none">Limited population (Chinese children)
Coretti et al. (2018)	<ul style="list-style-type: none">ASD: 11NC: 14	<ul style="list-style-type: none">ASD: 35 ± 5.7NC: 35 ± 8.4	<ul style="list-style-type: none">ASD: (9/2)NC: (8/6)	<ul style="list-style-type: none">Phylum level: ↓ <i>Actinobacteria</i>, ↑ in <i>Bacteroidetes</i> and <i>Proteobacteria</i><i>Firmicutes</i> represented the most abundant phylum in both ASD and NC PTs↑ <i>Bacteroidetes/Firmicutes</i> ratioFamily level: ↓ <i>Actinomycetaceae</i>, <i>Coriobacteriaceae</i>, <i>Bifidobacteriaceae</i>, <i>Gemellaceae</i>, and <i>Streptococcaceae</i>	<ul style="list-style-type: none">Observed a reassortment of the gut ecosystem in young ASD PTs↑ mucin-degrading <i>R. torques</i> in feces of ASD PTs↑butyrogenic <i>F. prausnitzii</i> and butyrate in ASD pts	<ul style="list-style-type: none">A limited number of evaluated children

(Continues)

TABLE 1 (Continued)

References	Sample size	Mean age in years ± SD (Range)	Gender (Male/ Female)	Changes in taxonomic composition (in PT compared to NC)	Association with clinical features (in PT compared to NC)	Limitations/Notes
Zhang et al. (2018)	<ul style="list-style-type: none">ASD: 35NC: 6	<ul style="list-style-type: none">ASD: 4.9 ± 1.5NC: 4.6 ± 1.1	<ul style="list-style-type: none">ASD: (29/6)NC: (5/1)	<ul style="list-style-type: none">Phylum level: ↑ <i>Bacteroidetes</i>/<i>Firmicutes</i> ratioGenus level: A relative ↑ of <i>Sutterella</i> and <i>Odoribacter</i> and significant ↑ <i>Butyrivimonas</i>↓ <i>Veillonella</i> and <i>Streptococcus</i>↓ Butyrate and lactate producers↓ diversity↑ mucin degraders and other SCFA producersRelative ↓ mucolytic <i>Akkermansia muciniphila bacterium</i>	<ul style="list-style-type: none">Abnormal intestinal permeability has been reported in PTsASD is positively correlated with periodontal, negatively related to type 1 diabetes↑ D-Arginine and D-ornithine metabolism, ether lipid metabolism, bacterial chemotaxis, neurodegenerative diseases, prion diseases, phosphotransferase system, and flagellar assembly genes in PT group↑ meiosis-yeast, steroid hormone biosynthesis, glycosaminoglycan degradation, and lipoic acid metabolism in the NC group	<ul style="list-style-type: none">Small sample sizeThe human-microbe disease association database used has not been updated since it was established
Strati et al. (2017)	<ul style="list-style-type: none">ASD: 40NC: 40	<ul style="list-style-type: none">ASD: 10 (5–17)NC: 7 (3.6–12)	<ul style="list-style-type: none">ASD: (31/9)NC: (28/12)	<ul style="list-style-type: none">↑ <i>Firmicutes</i>/<i>Bacteroidetes</i> ratioGenus level: ↓ <i>Alistipes</i>, <i>Bilophila</i>, <i>Dialister</i>, <i>Parabacteroides</i>, and <i>Veillonella</i>↑ <i>Collinsella</i>, <i>Corynebacterium</i>, <i>Dorea</i>, and <i>Lactobacillus</i>*Fungal alterations: genus <i>Candida</i> was one of the most abundant taxa in the gut mycobiota	<ul style="list-style-type: none">Constipation has a significant effect on the microbial community within NCs but not within PTsThe severity of the autistic phenotype does not affect the bacterial community	NA
Inoue et al. (2016)	<ul style="list-style-type: none">ASD: 6NC: 6	Infants (numbers NA)	NA	<ul style="list-style-type: none">Genus level: ↑ <i>Faecalibacterium</i>↓ <i>Blautia</i>	<p><i>Faecalibacterium</i> abundance was strongly correlated with a greater number of differentially expressed genes involved in both the interferon-γ-mediated signaling pathway and the type I interferon signaling pathway</p>	<ul style="list-style-type: none">Small sample sizeNo stratification for age and sex

(Continues)

TABLE 1 (Continued)

References	Sample size	Mean age in years ± SD (Range)	Gender (Male/Female)	Changes in taxonomic composition (in PT compared to NC)	Association with clinical features (in PT compared to NC)	Limitations/Notes
Tomova et al. (2015)	<ul style="list-style-type: none">• ASD: 10• Siblings: 9• NC: 10	<ul style="list-style-type: none">• ASD: (2–9)• Siblings: (5–17)• NC: (2–11)	<ul style="list-style-type: none">• ASD: (9/1)• Siblings: (7/2)• NC: 10 boys	<ul style="list-style-type: none">• ↓ <i>Bacteroidetes</i>/<i>Firmicutes</i> ratio• Phylum level: No difference in <i>Bacteroidetes</i> or <i>Firmicutes</i> phyla• Genus level: ↓ <i>Clostridia</i> and <i>Desulfovibrio</i>• ↓ <i>Bifidobacterium</i> in siblings than in ASD PTs	<ul style="list-style-type: none">• A very strong association of <i>Desulfovibrio</i> spp. with the severity of ASD• A strong positive correlation of ASD severity with the severity of GI dysfunction.• No correlation between plasma levels of oxytocin, testosterone, DHEA-S, and fecal microbiota were• ↑GI dysfunction in PTs as well as in their siblings• <i>Bacteroidetes</i>/<i>Firmicutes</i> ratio had a weak negative correlation with the severity of ASD• ↓ Level of oxytocin in the plasma of PTs and their siblings	<ul style="list-style-type: none">• Small sample size• No stratification for age or sex
De Angelis et al. (2013)	<ul style="list-style-type: none">• ASD: 10• other related disorders: 10• NC: 10	(4–10)	In total: (14/16)	<ul style="list-style-type: none">• <i>Faecalibacterium</i> and <i>Ruminococcus</i> were present at the highest in ASD• <i>Caloramator</i>, <i>Sarcina</i>, and <i>Clostridium</i> were the highest in ASD• Except for <i>Eubacterium siraeum</i>, the lowest level of <i>Eubacteriaceae</i> was found on fecal samples of AD children.• The level of <i>Bacteroidetes</i> genera and some <i>Alistipes</i> and <i>Akkermansia</i> species were almost the highest in ASD and related disorders children• <i>Sutterellaceae</i> and <i>Enterobacteriaceae</i> were higher in ASD• <i>Bifidobacterium</i> species decreased in ASD	NA	<ul style="list-style-type: none">• Small sample size• Demographic data are not fully detailed for each subgroup

(Continues)

TABLE 1 (Continued)

References	Sample size	Mean age in years ± SD (Range)	Gender (Male/Female)	Changes in taxonomic composition (in PT compared to NC)	Association with clinical features (in PT compared to NC)	Limitations/Notes
Finegold et al. (2010)	<ul style="list-style-type: none">ASD: 33siblings: 7NC: 8	(2–13)	<ul style="list-style-type: none">ASD: (24/9)siblings: (5/2)NC: (5/3)	<ul style="list-style-type: none">Phylum level: <i>Bacteroidetes</i> was found at high levels in the severely ASD PTs, while <i>Firmicutes</i> were more predominant in NCSmaller but significant differences in the <i>Actinobacterium</i> and <i>Proteobacterium</i> phyla.<i>Desulfovibrio</i> species and <i>Bacteroides vulgatus</i> are higher in ASD PTs	NA	<ul style="list-style-type: none">The immune status was not investigatedPyrosequencing is limited by normal primer biases as well as the incomplete nature of 16S rDNA databases
Parracho et al. (2005)	<ul style="list-style-type: none">ASD: 58siblings: 12NC:10	<ul style="list-style-type: none">ASD: (3–16)siblings: (2–10)NC: (3–12)	<ul style="list-style-type: none">ASD: (48/10)siblings: (7/5)NC: (6/4)	<ul style="list-style-type: none">Fecal flora of ASD PTs contained a higher incidence of the <i>Clostridium histolyticum</i> group (<i>Clostridium</i> clusters I and II) but healthy sibling group displayed intermediate levels.Healthy sibling group harbored the lowest levels of <i>Bacteroides</i> of all the subject groups.	<ul style="list-style-type: none">GI problems were associated with high levels of <i>Clostridia</i>.An association between high <i>Clostridial</i> counts and individuals consuming probiotics	NA
Sandler et al. (2000)	ASD: 11	ASD: 59 ± 13.3 (in months)	ASD: (10/1)	Only in 4 ASD children: Anaerobic cocci, chiefly <i>peptostreptococcal</i> species were absent	NA	<ul style="list-style-type: none">Small sample sizeNo controls
Ming et al. (2018)	<ul style="list-style-type: none">ADHD: 68NC: 72	<ul style="list-style-type: none">ADHD: 10.3 ± 2.97NC: 9.7 ± 3.24	<ul style="list-style-type: none">ADHD: (51/17)NC: (33/39)	Genus level: Slight ↑ in <i>Bifidobacterium</i>	<ul style="list-style-type: none">No significant relationship between medication and constipation, flatulence or total Gastrointestinal Severity IndexPTs had significantly ↑ mean Gastrointestinal Severity Index, constipation, and flatulence scores.	NA

Prehn-Kristensen et al. (2018)	<ul style="list-style-type: none">ADHD: 14NC: 17	<ul style="list-style-type: none">ADHD: 11.9 ± 2.5NC: 13.1 ± 1.7	Only males	<ul style="list-style-type: none">No difference in the observed species and Chao1 richness estimator while Shannon diversity was significantly ↓.Genus level: <i>Prevotella</i> and <i>Parabacteroides</i> were detected as markers for the NCs group and <i>Neisseria</i> for PTs.Family level: ↑<i>Prevotellaceae</i>, <i>Catabacteriaceae</i>, and <i>Porphyromonadaceae</i> for NCs and <i>Neisseriaceae</i> for PTs	<ul style="list-style-type: none">A correlation between the symptoms of hyperactivity and alpha diversity.	<ul style="list-style-type: none">No female PTs10 out of 14 PTs had taken methylphenidateSmall sample size
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(Continues)

TABLE 1 (Continued)

References	Sample size	Mean age in years ± SD (Range)	Gender (Male/Female)	Changes in taxonomic composition (in PT compared to NC)	Association with clinical features (in PT compared to NC)	Limitations/Notes
Aarts et al. (2017)	<ul style="list-style-type: none">• Microbiome analysis• ADHD: 19• NC: 77• fMRI analysis• ADHD: 24• NC: 63• Overlap• ADHD: 6• NC: 22	<ul style="list-style-type: none">• Microbiome analysis• ADHD: 19.5 ± 2.5• NC: 27.1 ± 14.3• fMRI analysis• ADHD: 20.3 ± 3.7• NC: 21.3 ± 3.4• Overlap• ADHD: 18.6 ± 2.5• NC: 21.1 ± 3.3	<ul style="list-style-type: none">• Microbiome analysis• ADHD: (13/6)• NC: (41/36)• fMRI analysis• ADHD: (18/6)• NC: (39/24)• Overlap• ADHD: (4/2)• NC: (13/9)	<ul style="list-style-type: none">• Phylum level: ↑ <i>Actinobacteria</i>, ↓ <i>Firmicutes</i>• Genus level: ↑ <i>Bifidobacterium</i>• Order level: ↓ <i>Clostridiales</i>	<ul style="list-style-type: none">• Significant ↑ cyclohexadienyl dehydratase (CDT) enzyme (involved in the production of phenylalanine, tyrosine, or tryptophan)• A negative association of CDT with reward anticipation responses in the bilateral ventral striatum	<ul style="list-style-type: none">• The microbiome shotgun sequencing method could have been combined with a proteomics/metabolomics approach• 25% of NCs were siblings of ADHD cases, and another sub-sample of the control group did not undergo clinical screening for ADHD• The NCs group was significantly older than the PT group
Nguyen et al. (2019)	<ul style="list-style-type: none">• SZ: 25• NC: 25	<ul style="list-style-type: none">• SZ: 52.9 ± 11.2• NC: 54.7 ± 10.7	<ul style="list-style-type: none">• SZ: (11/14)• NC: (10/15)	<ul style="list-style-type: none">• Phylum level: ↓ <i>Proteobacteria</i>• Genus level: ↑ <i>Anaerococcus</i>, ↓ <i>Haemophilus</i>, <i>Sutterella</i>, and <i>Clostridium</i>	<ul style="list-style-type: none">• ↑ Depressive symptoms with genus <i>Bacteroides</i>• ↑ Negative symptoms with ↓ family <i>Ruminococcaceae</i>• Mental well-being was positively correlated with phylum <i>Verrucomicrobia</i>	<ul style="list-style-type: none">• Cross-sectional• Small sample size• Not considering Comorbid medical illnesses
Shen et al. (2018)	<ul style="list-style-type: none">• SZ: 64• NC: 53	<ul style="list-style-type: none">• SZ: 42 ± 11• NC: 39 ± 14	<ul style="list-style-type: none">• SZ: (36/28)• NC: (35/18)	<ul style="list-style-type: none">• Phylum level: ↑ <i>Proteobacteria</i>, <i>Fusobacteria</i>• Genus level: ↑ <i>Succinivibrio</i>, <i>Megasphaera</i>, <i>Collinsella</i>, <i>Clostridium</i>, <i>Klebsiella</i>, and <i>Methanobrevibacter</i>• ↓ <i>Blautia</i>, <i>Coproccoccus</i>, and <i>Roseburia</i>	<ul style="list-style-type: none">• Several metabolic pathways differed significantly: Vitamin B6, fatty acid, starch and sucrose, tryptophan, cysteine, methionine, and linoleic acid metabolism, as well as the degradation of some xenobiotics	<ul style="list-style-type: none">• Cross-sectional• Small sample size• Limited population (Chinese Han nationality)• Not completely eliminating antipsychotics' effect
Castro-Nallar et al. (2015)	<ul style="list-style-type: none">• SZ: 16• NC: 16	<ul style="list-style-type: none">• SZ: 34.7 ± 4.8• NC: 34.3 ± 10.1	<ul style="list-style-type: none">• SZ: (9/7)• NC: (9/7)	<ul style="list-style-type: none">• Phylum level: ↑ <i>Firmicutes</i>, <i>Bacteroidetes</i>, and <i>Actinobacteria</i>• Species level: ↓ species number• ↑ Lactic acid bacteria: <i>Lactobacillus gasseri</i> was 400 times more abundant• ↑ <i>Streptococcus gordonii</i>, <i>Streptococcus thermophilus</i> and <i>Streptococcus sp.</i>	<ul style="list-style-type: none">• ↑ Several metabolic pathways: saccharide, polyol, and lipid transport systems, peptide and nickel transport, metallic cation, iron-siderophore, and vitamin B12 transport and phosphate and amino acid transport including glutamate transport.• ↓ Several metabolic pathways: energy, carbohydrate and lipid metabolism	

(Continues)

TABLE 1 (Continued)

References	Sample size	Mean age in years ± SD (Range)	Gender (Male/Female)	Changes in taxonomic composition (in PT compared to NC)	Association with clinical features (in PT compared to NC)	Limitations/Notes
Yolken et al. (2015)	• SZ: 41	• SZ: 39.2 ± 9.9	• SZ: (27/14)	Phiadh level: ↑ <i>Lactobacillus</i> phage phiadh	• Phiadh level was associated with the administration of Valproate • ↑ comorbid immunological disorders in PTs	• Limited sample sizes
	• NC: 33	• NC: 30.9 ± 8.8	• NC: (19/14)			
Coello et al. (2019)	• BD: 113	• BD: 31 (26–39)	• BD: (43/70)	Genus level: <i>Flavonifractor</i> was present in 61% of BD PTs, 42% of UR and 39% of NC. In BD PTs, it was associated with smoking and female sex	• <i>Flavonifractor</i> which may induce oxidative stress and inflammation in its host was associated with BD.	• Cross-sectional • Small UR sample size • Self-reported physical activity • No dietary information • No information on bowel movements/stool consistency
	• UR: 39 • NC: 77	• UR: 28 (22–34) • NC: 29 (24.5–40.5)	• UR: (18/21) • NC: (30/47)			
Aizawa et al. (2019)	• BD: 39	• BD: 40.3 ± 9.2	• BD: (17/22)	• No significant difference was found in either bacterial counts between the two groups • A significant negative correlation between <i>Lactobacillus</i> counts and sleep ($p = 0.01$) • A significant negative correlation between <i>Bifidobacterium</i> but not <i>Lactobacillus</i> counts and cortisol levels ($p = 0.02$) in BD PTs	• <i>Bifidobacterium</i> or <i>Lactobacillus</i> counts may not play a major role in the pathophysiology of BD in this cohort • Possible roles of these bacteria in sleep and stress response of the BD PTs	• The severity of BD in the subjects was relatively mild • No detailed counts of different species of <i>Bifidobacterium</i> or <i>Lactobacillus</i> • The cross-sectional design of the present study makes it difficult to determine whether the observed relationships were the causes or effects of the illness.
	• NC: 58	• NC: 43.1 ± 12.9	• NC: (22/36)			
Painold et al. (2018)	• BD: 32	• BD: 41.3 ± 14.7	• BD: (18/14)	• Phylum level: ↑ <i>Actinobacteria</i> and <i>Coriobacteria</i> (class) • Genus level: ↓ <i>Ruminococcaceae</i> and <i>Faecalibacterium</i>	• A negative correlation between microbial alpha-diversity and illness duration • Identified bacterial classes associated with inflammatory status, serum lipids, TRP, depressive symptoms, oxidative stress, anthropometrics, and metabolic syndrome in BD PTs	• Cross-sectional • Small sample size • All BD PTs were in an acute episode of bipolar depression. • No explicit assessment/standardization of diet/lifestyle parameters
	• NC: 10	• NC: 31.4 ± 7.6	• NC: (4/6)			

(Continues)

TABLE 1 (Continued)

References	Sample size	Mean age in years ± SD (Range)	Gender (Male/ Female)	Changes in taxonomic composition (in PT compared to NC)	Association with clinical features (in PT compared to NC)	Limitations/Notes
Schwarz et al. (2018)	FEP: 28 NC: 16	FEP: 25.9 ± 5.5 NC: 27.1 ± 6.0	FEP: (16/12) NC: (8/8)	<ul style="list-style-type: none">• Family level: ↑ <i>Lactobacillaceae</i>, <i>Halothiobacillaceae</i>, <i>Brucellaceae</i> and <i>Micrococcineae</i>, ↓ <i>Veillonellaceae</i>• Genera: ↑ <i>Lactobacillus</i>, <i>Tropheryma</i>, <i>Halothiobacillus</i>, <i>Saccharophagus</i>, <i>Ochrobactrum</i>, <i>Deferribacter</i>, and <i>Halorubrum</i>, ↓ <i>Anabaena</i>, <i>Nitrosospora</i> and <i>Gallionella</i>	<i>Lachnospiraceae</i> , <i>Bacteroides</i> spp., <i>Lactobacillus</i> were correlated with ↑ psychotic symptoms	<ul style="list-style-type: none">• Small sample size• No community-level characteristics reported• A model predicting remission only used the top 5 families rather than the entire population
Evans et al. (2017)	<ul style="list-style-type: none">• BD: 115• NC: 64	<ul style="list-style-type: none">• BD: 50.2 ± 12.8• NC: 48.6 ± 16.6	<ul style="list-style-type: none">• BD: (32/83)• NC: (24/40)	<ul style="list-style-type: none">• Genus level: ↓ <i>Faecalibacterium</i>• ↓ unclassified (Family level: <i>Ruminococcaceae</i>)	<i>Faecalibacterium</i> was associated with improved physical health, depression, and sleep quality scores; <i>Anaerostipes</i> and <i>Ruminococcaceae</i> family were associated with improved physical health, while an unclassified genus from the family <i>Enterobacteriaceae</i> was associated with worse physical health scores	<ul style="list-style-type: none">• Cross-sectional• Inability to control for medication use and compliance
Flowers et al. (2017)	<ul style="list-style-type: none">• BD on AP: 46• BD off AP: 69	<ul style="list-style-type: none">• BD on AP: 46.0 ± 12.0• BD off AP: 51.7 ± 13.5	<ul style="list-style-type: none">• BD on AP: (12/34)• BD off AP: (21/48)	<ul style="list-style-type: none">• AP-treated PTs: ↑ <i>Lachnospiraceae</i>• Non-AP-treated PTs: ↑ <i>Akkermansia</i> and <i>Sutterella</i>	<ul style="list-style-type: none">• ↓ <i>Akkermansia</i> in non-obese AP-treated PTs	<ul style="list-style-type: none">• Illness' duration, disease's indicators, and symptom severity were not considered.• Comorbid medical conditions/other metabolic biomarkers effect on microbiome needed further investigation.• No dietary information

Note: All studies are arranged in a reversed chronological order (from the newest to oldest) per diagnosis. Abbreviations: ↑ indicates an increase; ↓ indicates a decrease; ADHD, attention deficit hyperactivity disorder; AP, antipsychotics; ASD, autism spectrum disorder; BD, bipolar disorder; FEP, first episode patients; GI, gastro-intestinal; NA, not available; NC, non-neuropsychiatric comparison subject; PT, patient; SZ, schizophrenia; UR, unaffected first degree relative.

the density of microglia, mostly in the temporal cortex, and on the molecular level an overall increase in expression of pro-inflammatory genes on both transcript and protein levels (van Kesteren et al., 2017) together with an increase in microglial markers (Barichello, Simoes, Quevedo, & Zhang, 2019). Interestingly, in live human subjects with SZ or BD, C4A mRNA expression in peripheral blood mononuclear cells predicts the presence and severity of delusions (Melbourne, Rosen, Feiner, & Sharma, 2018).

For ASD, the increase in brain volume in some children with ASD manifestations is frequently associated with excessive activation of microglia in regions with an overabundance of cortical neurons and connections (Morgan et al., 2010; Redcay & Courchesne, 2005; Sacco, Gabriele, & Persico, 2015; Suzuki et al., 2013; Walker et al., 2012). Genes associated with the functioning of microglia have shown higher expression levels in brain samples from patients with ASD in comparison to controls (Parikshak et al., 2016), and gene co-expression network analysis of postmortem ASD brain tissue identified an upregulation of glial markers in the cortex, along with a downregulation of a module containing synaptic genes, compared with typically developing individuals (Voineagu et al., 2011). Moreover, genes that regulate the development of microglia are more activated in males (Werling, Parikshak, & Geschwind, 2016) who suffer from ASD more frequently compared to females with a ratio of 4:1 (Fombonne, 2009; Gillberg, Cederlund, Lamberg, & Zeijlon, 2006). In addition, the DNA methylation of genes known to be the modulators of the microglial activity or implicated in synaptic pruning has been found to be dysregulated in patients with ASD (Nardone et al., 2014; Prinz & Priller, 2014).

Autophagy also appears to be an essential component of microglia-mediated synaptic pruning (Plaza-Zabala, Sierra-Torre, & Sierra, 2017). Deletion of *Atg7*, an autophagy gene, specifically in microglia abolished its ability to prune synapses, resulting in an increase in dendritic spines with immature filopodia-like structures which may contribute to ASD pathogenesis by affecting the social behavior circuit (Kim et al., 2017). Another study revealed that some children with ASD had overactive mTOR, a protein which prohibits the autophagy from cleaning the area and disposing of the damaged synapses (Tang et al., 2014). Immunohistochemical studies have shown that the brain tissue and cerebrospinal fluid samples from patients with ASD showed an abundance of activated microglia in the cerebral cortex, white matter, and cerebellum (Vargas, Nascimbene, Krishnan, Zimmerman, & Pardo, 2005). Furthermore, ASD postmortem brain tissues exhibited a decreased number of inactivated microglia in the grey and white matters and increased numbers of activated microglia in the grey matter (Lee, Azmitia, & Whitaker-Azmitia, 2017).

5 | THE LINK BETWEEN INTESTINAL MICROBIOTA DYSBIOSIS AND MICROGLIAL DYSFUNCTION IN NEUROPSYCHIATRIC DISORDERS

The bidirectional communication between microbiota, the different phyla and bacterial species in the GI system, and the brain

has drawn much attention in recent years. Several studies in mice showed significant effects of the different microbiota compositions on early life control of emotions like anxiety, motor activity, and cognitive functions (Clarke et al., 2013; Desbonnet, Clarke, Shanahan, Dinan, & Cryan, 2014; Diaz Heijtz, 2016; Neufeld, Kang, Bienenstock, & Foster, 2011), confirming a functional connection between the microbiota and brain. Studies mostly from the microbiota-devoid germ-free mice or mice treated with broad-spectrum antibiotics have shown that specific microbiota can impact brain physiology and neurochemistry and exhibit structural changes in the brain (Dinan & Cryan, 2017; Fung, Olson, & Hsiao, 2017; Martin & Mayer, 2017; Principi & Esposito, 2016; Zhang et al., 2015) and neurological deficiencies in learning, memory, recognition, and emotional behaviors (Foster, Rinaman, & Cryan, 2017; Gareau et al., 2011; Smith, 2015), along with less social behaviors (Mayer, Tillisch, & Gupta, 2015; Schumann & Amaral, 2006; Vuong, Yano, Fung, & Hsiao, 2017).

In the general population, it is believed that brain development is influenced by the intestinal microbiota *via* several immunological and signaling pathways (for a review, see [Ma et al., 2019]). Moreover, the intestinal microbiota can modulate neurogenesis in the brain as demonstrated by the promotion of fetal neural development by some regulators from gut bacteria, which have a potential impact on cognitive function during adulthood (Humann et al., 2016; Rolls et al., 2007). The blood-brain barrier and vagus nerve actively participate in the bidirectional interactions between the intestinal microbiota and brain to maintain their homeostasis (Bonaz, Sinniger, & Pellissier, 2017; Braniste et al., 2014; Forsythe, Bienenstock, & Kunze, 2014).

Recently, the microbiota have shown an impact on the properties and function of microglia. For instance, with the absence of microbiota, microglia in germ-free mice displayed alteration in their morphological characteristics and gene expression profiles, accompanied by inhibition in their maturation state in the brain cortex (Erny et al., 2015). This can indicate that the intestinal microbiota contribute directly to the maturation progress of naïve microglia (Ma et al., 2019). In another study, it has been shown that microglia respond to microbiota change in a sex- and time-dependent manner from prenatal stages (Thion et al., 2018). In a very recent study, the manipulation of microbiota in antibiotic-treated or germ-free adult mice resulted in significant deficits in fear extinction learning combined by an immature state and a change in gene expression in microglia (Chu et al., 2019). These microglial differentially expressed genes were found to be enriched in pathways related to synapse organization and synapse assembly, suggesting that deliberate manipulation of the microbiota may alter microglia-mediated synaptic pruning and disrupt dendritic spine remodeling, causing behavioral abnormalities. By re-colonizing germ-free mice with a complete microbiota from healthy control mice immediately after birth, but not after weaning, the extinction learning ability was restored, indicating that the extinction learning and learning-related plasticity require microbiota-derived signals during a critical developmental period before weaning (Chu et al., 2019).

TABLE 2 Most recent meta-analyses or reviews of meta-analyses on clinical trials of dietary intervention in individuals diagnosed with autism spectrum disorder, attention deficit hyperactivity disorder, schizophrenia, or bipolar disorder

Reference	Clinical studies (n)	Sample size (INT/PL)	Mean age in years (range)	Gender (M/F)	Dietary intervention (mean intervention time, range)	Overall difference and association with clinical features between INT and placebo groups	Difference and association with clinical features between INT and placebo groups per dietary intervention	Limitations/Notes
Fraguas et al. (2019)	27	ASD: 1,028 (542/386)	7.1 (2–60)	89.1%/ 10.9% (100%-25%)	<ul style="list-style-type: none">• Omega-3 polyunsaturated fatty acids• Vitamin supplementation• Other• 10.6 weeks (1–24 weeks)	<ul style="list-style-type: none">• Associated symptoms ($p < 0.001$)• Autism global ($p = 0.002$)• Clinical impression ($p = 0.006$)• Core symptoms ($p = 0.009$)• Clinical impression ($p < 0.001$)	<ul style="list-style-type: none">• Omega-3:• Associated symptoms ($p = 0.046$)• Core symptoms ($p = 0.042$) Vitamin: <ul style="list-style-type: none">• Associated symptoms ($p = 0.009$)• Clinical impression ($p = 0.042$)• Core symptoms ($p = 0.011$)	<ul style="list-style-type: none">• Methodologic heterogeneity in intervention, clinical measurements, outcomes, and sample characteristics
Chang, Su, Mondelli, and Pariante (2018)	7	ADHD: 534	~9.41	~78.79%/~21.21%	Omega-3 polyunsaturated fatty acids	<ul style="list-style-type: none">• Associated symptoms ($p < 0.0001$)• Inattention ($p = 0.0001$),• Hyperactivity ($p = 0.04$)	NA	<ul style="list-style-type: none">• Placebo-controlled• Limited amount of studies
Pelsser et al. (2017)	14 (6 meta-analyses)	ADHD: 1937 (NA)	NA	NA	<ul style="list-style-type: none">• Omega-3 and/or omega-6• Few foods diet• Artificial food coloring	NA	NA	<ul style="list-style-type: none">• Systematic review of meta analyses• The effect on symptoms and cognition is not reported
Aucoin, LaChance, Cooley, and Kidd (2018)	822	SZ (NA)	NA	NA	<ul style="list-style-type: none">• Carbohydrates and fiber• Fats• Protein• Gluten• Pre/probiotics• Vegetables and fruits• Phytonutrients• Minerals• Vitamins	NA	<p>High intake associated with psychosis:</p> <ul style="list-style-type: none">• (fat) dairy, fish, red meat, olive oil, reduced-caloric butter/margarine <p>Low intake associated with psychosis:</p> <ul style="list-style-type: none">• Milk, fish, red meat, potato, nuts, pulses, chicken	

(Continues)

TABLE 2 (Continued)

Reference	Clinical studies (n)	Sample size (INT/PL)	Mean age in years (range)	Gender (M/F)	Dietary intervention (mean intervention time, range)	Overall difference and association with clinical features between INT and placebo groups	Difference and association with clinical features between INT and placebo groups per dietary intervention	Limitations/Notes
Arroll et al. (2014)	21	SZ: 1,212 (NA)	NA	NA	• Omega 3 and/or omega 6 • N-Acetyl cysteine • Alpha-lipoic acid • Vitamin C & E • Vitamin B, Folate • L-theanine	NA	NA	• Review, it did not include meta-analyses • Limitations of the included studies are not listed • The results are not quantified
Bauer et al. (2016)	6	BD: 296	Mean age range: 28.87 (SD = 7.86)–60 (SD = 6.7)	82.77%/17.23% (100%–50%)	(Specific dietary intervention is not provided)	NA	In the included studies with dietary intervention, depression symptoms and cognitive functioning were improved	Except for nutritional intervention, other lifestyle interventions are also included

Note: Publications are arranged in a reversed chronological order (from newest to oldest) per diagnosis.

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; BD, bipolar disorder; INT, intervention; NA, not available; NC, non-neuropsychiatric comparison subject; PL, placebo; PT, patient; SZ, schizophrenia.

In humans, the intestinal microbiota have been shown to modulate the microglial activation and function during developmentally sensitive periods (Erny et al., 2015). The change in microglial activity can have a direct effect on neuronal circuits function *via* synaptic pruning alteration (Tognini, 2017). It is probably not a coincidence that synaptic pruning occurs during the same time as the maturation of the intestinal microbiota (Figure 1; Agans et al., 2011). Indeed, in a recent study in rats using diffusion tensor imaging, the intestinal microbiota have shown an association with structure-specific changes in white matter architecture in the brain *via* modulation of synaptic pruning (Ong et al., 2018), which can influence the brain development and function. Moreover, several studies found evidence that the development of the early postnatal nervous system and brain plasticity is influenced by the intestinal microbial status (Collins, Borojevic, Verdu, Huizinga, & Ratcliffe, 2014; Lu et al., 2018; Sudo et al., 2004). In addition, a decreased stability and diversity of the intestinal microbiota accompanied by aging parallels grey and white matter volume loss (Bartzokis et al., 2003; Ge et al., 2002) and a decrease in cognitive function (Harada, Natelson Love, & Triebel, 2013; Luo & Craik, 2008; Salthouse, 2012). This is supported by the observed associations between microbiota perturbation and neuropsychiatric disorders and their respective severities (Cryan & Dinan, 2015; Rogers et al., 2016) including ASD (Coretti et al., 2018; De Angelis et al., 2013; de Theije et al., 2014; Finegold et al., 2010; Hsiao et al., 2013; Hughes, Rose, & Ashwood, 2018; Inoue et al., 2016; Li, Han, Dy, & Hagerman, 2017; Mayer, Padua, & Tillisch, 2014; Parracho, Bingham, Gibson, & McCartney, 2005; Sandler et al., 2000; Strati et al., 2017; Tomova et al., 2015; Wang, Zhou, et al., 2019; Zhai et al., 2019; Zhang, Ma, Zhang, He, & Wang, 2018; for reviews, see Madore et al., 2016; Srikantha & Mohajeri, 2019; Vuong & Hsiao, 2017), ADHD (Aarts et al., 2017; Cenit, Nuevo, Codoner-Franch, Dinan, & Sanz, 2017; Ming et al., 2018; Prehn-Kristensen et al., 2018; Richarte et al., 2018), SZ (Castro-Nallar et al., 2015; Fond et al., 2015; Nemani et al., 2015; Nguyen, Kosciolk, Eyler, Knight, & Jeste, 2018; Schwarz et al., 2018; Severance, Prandovszky, Castiglione, & Yolken, 2015; Shen et al., 2018; Yolken et al., 2015; for reviews, see Rodrigues-Amorim et al., 2018; Yuan, Kang, Zhuo, Huang, & Song, 2019) and BD (Aizawa et al., 2019; Coello et al., 2019; Evans et al., 2017; Flowers, Evans, Ward, McInnis, & Ellingrod, 2017; Nguyen et al., 2018; Painold et al., 2018; Schwarz et al., 2018; Yolken & Dickerson, 2017; for a total summary of the aforementioned neuropsychiatric disorders, see Table 1).

6 | IMPROVING THE INTESTINAL MICROBIOTA COMPOSITION AS A SUPPORTIVE THERAPEUTIC APPROACH FOR NEUROPSYCHIATRIC DISORDERS

Since the intestinal microbiota have been associated with microglial modulation and neuronal development, the modification of the microbiota composition represents a promising therapeutic target for patients with neuropsychiatric disorders (Genedi, Janmaat,

Haarman, & Sommer, 2019). Improving the microbiota composition could benefit the host via two main mechanisms; per improvement in neuropsychiatric symptoms severity and/or by alleviating intestinal complaints. In the aforementioned neuropsychiatric disorders, comorbidity with GI symptoms is observed. Constipation is a prevalent symptom in individuals diagnosed with SZ (De Hert, Dockx, et al., 2011; De Hert, Hudyana, et al., 2011; Koizumi et al., 2013), which may be secondary to factors as antipsychotic use, diet, and sedentary lifestyle. Patients with BD who use lithium often experience diarrhea (Gitlin, 2016). GI symptoms in children with ASD are common and often linked to the children's abnormal behavior and social interaction deficits (Critchfield, van Hemert, Ash, Mulder, & Ashwood, 2011; Navarro, Liu, & Rhoads, 2016; Tomova et al., 2015). These symptoms include constipation, abdominal pain, and diarrhea (Chandler et al., 2013), with constipation being one of the most commonly reported (Gorrindo et al., 2012). In children with ADHD, significantly higher means in the scores of the Gastrointestinal Severity Index, constipation and flatulence were found in comparison to a non-psychiatric comparison group (Ming et al., 2018). Both neuropsychiatric symptoms and GI complaints form a burden on the patient. Improvement in just one of these burdens can make a difference in the subjective well-being and quality of life. Besides that, improvement in GI functions can lead to higher compliance in the usage of psychopharmacological treatments (e.g., antipsychotics) in SZ and BD by alleviating the GI-related side effects.

It has been proposed, by multiple indications, that the intestinal microbiota can be modulated in multiple ways, successfully influencing symptoms in several neurological disorders. A comprehensive study reviewing modification of the intestinal microbiota shows that the supplementation of pro- and prebiotics, fecal transplantation, as well as dietary interventions are promising methods for enhancing the symptoms of some neurological disorders including ASD, anxiety disorder, depression, cognitive dysfunction in Alzheimer's disease, and possibly anorexia nervosa (Larroya-Garcia et al., 2019).

6.1 | Dietary intervention

Rapid changes in the microbiota composition can be driven by a change in the diet (David et al., 2014; Turnbaugh et al., 2009; Wu et al., 2011), mainly by altering the quality and quantity of dietary fat, fibers, and carbohydrates (Fava et al., 2013; Flint, Duncan, Scott, & Louis, 2007; Sonnenburg et al., 2010). Therefore, modifying the diet may prove an easy way to improve the condition and quality of life of neuropsychiatric patients. Dietary supplementation including omega-3 fatty acids and vitamin supplementation, known to have an impact on microbiota composition (Costantini, Molinari, Farinon, & Merendino, 2017; Ribeiro, Nicoli, Santos, & Lima-Santos, 2019; Tabatabaeizadeh, Tafazoli, Ferns, Avan, & Ghayour-Mobarhan, 2018), were more efficacious than the placebo at improving several ASD symptoms (for a meta-analysis of double-blind, randomized clinical trials, see [Fraguas et al., 2019]; Table 2). Different clinical studies were performed on participants

with ADHD to evaluate the efficacy of different diet interventions and restricted elimination diets (for reviews, see Heilskov Rytter et al., 2015; Nigg & Holton, 2014; Pelsser, Frankena, Toorman, & Rodrigues Pereira, 2017; Stevenson et al., 2014; Table 2). Other clinical studies revealed that nutritional approaches including antioxidant and vitamin B supplementation, neuroprotective and anti-inflammatory nutrients can be used as an adjunct to antipsychotic medication in patients with SZ (for a meta-analysis, see [Arroll, Wilder, & Neil, 2014]; Table 2). A change in the diet showed promising results in reducing the risk of comorbid ailments in BD and improved the effectiveness of treatment by increasing the patient's sense of control and coping (for reviews, see Bauer et al., 2016; Lojko, Stelmach-Mardas, & Suwalska, 2018; Lopresti & Jacka, 2015; Teasdale et al., 2019; Tully et al., 2018; Table 2). In general, the quality of diet has been shown to have an inverse relationship to the symptoms' severity of mental illness (Florez, Dubowitz, Ghosh-Dastidar, Beckman, & Collins, 2015; Huddy et al., 2016; Mihrshahi, Dobson, & Mishra, 2015; Rienks, Dobson, & Mishra, 2013; for reviews, see Bruce-Keller, Salbaum, & Berthoud, 2018; Dawson, Dash, & Jacka, 2016). Currently, there are few randomized placebo-controlled dietary intervention studies, mainly explained by the fact that individuals in neuropsychiatric diagnoses often take different medications that can influence the microbiota composition. In general, a randomized, placebo study design and supplying a controlled diet for a significant amount of time in human participants are hardly feasible, which makes it hard to control for co-founding factors. As there are promising results, more studies should be performed to confirm these findings and clarify the extent to which past dietary habits of these patients groups and how the introduction of dietary interventions may affect the pathophysiology, progression, and treatment of neuropsychiatric disorders.

6.2 | Probiotics and prebiotics

Another way to modify the intestinal microbiota composition is mediated by the supplementation of probiotics, the living microorganisms which can provide a benefit to the host when administered in adequate amounts (Butel, 2014). The main bacterial genera used as probiotics in both animal and human studies are the *Lactobacillus* and *Bifidobacterium* genera (Genedi et al., 2019). Probiotics have been shown to boost the brain-derived neurotrophic factor (BDNF; Jeong, Kim, Hwang, Han, & Kim, 2016; Ranuh et al., 2019) that promotes the survival of existent neurons and enhance the neurogenesis (Liu & Nusslock, 2018; Numakawa, Odaka, & Adachi, 2017, 2018; Scharfman et al., 2005), thus playing an essential role in the normal neurological development (Larroya-Garcia et al., 2019). When levels of BDNF are low, problems in learning and/or memory arise (Numakawa, 2014; Numakawa et al., 2014). Studies involving animal models demonstrated that probiotics improved cognition, mood, anxiety, and stress (Ait-Belgnaoui et al., 2014; Bravo et al., 2011; Bruce-Keller et al., 2018; Chunchai et al., 2018; Desbonnet

et al., 2010; Mohle et al., 2016; Smith et al., 2014; Sudo et al., 2004). In humans, clinical studies have suggested that probiotics are beneficial in treating several psychological symptoms such as depression (Wallace & Milev, 2017), anxiety (Ng, Peters, Ho, Lim, & Yeo, 2018), and stress (Kato-Kataoka et al., 2016). Moreover, randomized trials have shown an influence of probiotics, in particular, on mood (Messiaoui et al., 2011; Steenbergen, Sellaro, van Hemert, Bosch, & Colzato, 2015). The probiotic supplementation has shown an improvement in constipation in different populations (Chmielewska & Szajewska, 2010; Dimidi, Christodoulides, Fragkos, Scott, & Whelan, 2014; Miller & Ouwehand, 2013) and is recognized to be efficacious for diarrhea and disturbed GI satiety signals (Sherwin, Sandhu, Dinan, & Cryan, 2016). Regarding the effect of probiotic administration on neuropsychiatric disorders, Dinan et al. proposed the concept of "Psychobiotics" to emphasize the potential of probiotics in the treatment of mental disorders (Dinan, Stanton, & Cryan, 2013). Five clinical studies on SZ were published but showed inconsistent results regarding the enhancement of neuropsychiatric symptoms (Dickerson et al., 2014; Ghaderi et al., 2019; Okubo et al., 2018; Severance et al., 2017; Tomasik, Yolken, Bahn, & Dickerson, 2015). Moreover, two studies were published targeting individuals with BD (Dickerson et al., 2018; Reininghaus et al., 2018; for an overview of clinical studies with probiotic intervention in SZ and BD, see [Genedi et al., 2019]; for a summary, see Table 3).

In different mouse models of ASD, autistic-like symptoms were improved by the administration of probiotics (Buffington et al., 2016; Hsiao et al., 2013; Sgritta et al., 2019; Wang, Yang, Zhang, Yu, & Yao, 2019). The probiotic intervention has shown influences on several neuroactive metabolites such as serotonin (Israelyan & Margolis, 2018) that is mainly produced in the intestine by intestinal bacteria (Larroya-Garcia et al., 2019). In individuals diagnosed with ASD, there is hyperactivation of a gene that codes for serotonin reuptake transporters (Israelyan & Margolis, 2018). In ASD, clinical studies with probiotic interventions showed promising results including better cognitive development and improvement in the Autism Diagnostic Observation Schedule, widely used to assess the core autism symptomatic behaviors (Adams, Johansen, Powell, Quig, & Rubin, 2011; Grossi, Melli, Dunca, & Terruzzi, 2016; Kaluzna-Czaplinska & Blaszczyk, 2012; Liu et al., 2019; Parracho et al., 2010; Sanctuary et al., 2019; Santocchi et al., 2016; Shaaban et al., 2018; Tomova et al., 2015; West Md & Roberts, 2013; for a summary, see Table 3). In the field, 95 out of 500 physicians reported using probiotics in treating children with ASD (Golnik & Ireland, 2009). Recently, other clinical studies are in the process from NIH (for more information, check <https://clinicaltrials.gov/ct2/results?cond=ASD&term=probiotic&cntry=&state=&city=&dist=>).

In individuals with ADHD, the probiotic supplementation combined with additional nutritional supplements were shown to be just as effective at improving symptoms as treatment with methylphenidate (Harding, Judah, & Gant, 2003). Another randomized clinical trial supports the beneficial role of probiotics in alleviating ADHD symptoms (Partty, Kalliomaki, Wacklin, Salminen, & Isolauri, 2015; for a summary of clinical studies, see Table 3). Nowadays, there are

other ongoing clinical studies to test the efficacy of probiotic on improving ADHD symptoms (for more information, check <https://clinicaltrials.gov/ct2/results?cond=Adhd&term=probiotic&cntry=&state=&city=&dist=>).

The use of prebiotics, the non-digestible plant-based carbohydrates that serve as nutrition for resident bacteria, increases the beneficial microbiota and attenuates stress behaviors in rodents (Burokas et al., 2017; Mika et al., 2017). In humans, a randomized trial revealed an improvement in the emotional affect and modulation of stress response following galacto-oligosaccharide supplementation in healthy volunteers (Schmidt et al., 2015). Combining diet restriction and a 6-week Bimuno® galacto-oligosaccharide (B-GOS®) prebiotic intervention in autistic children have revealed significantly lower scores of abdominal pain and improvement on bowel movement in addition to observed improvements in social behavior (Grimaldi et al., 2018).

6.3 | Fecal microbiota transplantation

Although not as widely used as diet, probiotics and prebiotics, fecal microbiota transplantation (FMT) is another procedure to modify the dysbiotic intestinal microbiota toward a balanced one (Evrensel & Ceylan, 2016). A large number of commensal microbes can be introduced orally or through enemas or colonoscopy into recipient patients. FMT is commonly used in the treatment of GI diseases such as *Clostridium difficile* infection, Crohn's disease, and ulcerative colitis (Anderson, Edney, & Whelan, 2012; Aroniadis & Brandt, 2013; Xu et al., 2015). A study reported that FMT from depressed individuals causes depression-like behaviors in mice (Gareau et al., 2011; Huo et al., 2017). Moreover, obese-type intestinal microbiota induce neurobehavioral changes in the absence of obesity which is linked to the prevalence of mental illness, particularly depression and dementia (Bruce-Keller et al., 2015). According to a preliminary study including six anxiety patients aged between 36 and 83, FMT has shown a 70% improvement in anxiety (Zamudio-Tiburcio et al., 2017). In an open-label study of FMT combined with antibiotics, a bowel cleanse and a stomach-acid suppressant, significant improvements in GI symptoms, ASD-related symptoms, and intestinal microbiota were observed (Kang et al., 2017). The follow-up on the same participants after 2 years of treatment revealed maintenance of the improvements in GI symptoms and ASD-related symptoms with significant increases in bacterial diversity and relative abundances of *Bifidobacteria* and *Prevotella* (Kang et al., 2019). Although these results are promising, caution needs to be taken as this trial was not placebo-controlled, blinded, nor randomized; and further trials are needed to confirm the therapeutic benefit and long-term safety of FMT for neuropsychiatric disorders.

The change in microbiota composition via dietary intervention, probiotic, and prebiotic has shown a direct effect on microglial activation and synaptic structures. Previous studies on rodents demonstrated that a consumption of high-fat diet caused a structural change in microglia as indicated by a significantly increased soma

TABLE 3 Clinical trials on probiotic supplementation in patients with autism spectrum disorder, attention deficit hyperactivity disorder, schizophrenia, or bipolar disorder

Reference	Sample size (INT/PL)	Mean age in years ± SD	Gender (M/F)	Study compound (way of administration: orally)	Biomarker(s)/outcome measurements	Difference between INT and placebo groups	Association with clinical features	Limitations/Notes
Sanctuary et al. (2019)	ASD: 8	6.8 ± 2.4 (3.9–10.9)	INT: (7/1)	<ul style="list-style-type: none">A probiotic (<i>Bifidobacterium infantis</i>) in combination with a bovine colostrum product (BCP) as a source of prebiotic oligosaccharidesThis 12-week study included 5 weeks of probiotic-prebiotic supplementation, followed by a 2-week washout period, and 5 weeks of prebiotic only supplementation	<ul style="list-style-type: none">CHARGEGastrointestinal History (GIH) surveyQuestionnaire on Pediatric Gastrointestinal Symptoms-Rome III Version (QPGS-RIII)Aberrant Behavior Checklist (ABC)The Repetitive Behavior Scale-Revised (RBS-R)The Adaptive Behavior Assessment System-Second Edition (ABAS-II)Microbial community state analysisBlood testsSerum, urinary and fecal metabolomics	<ul style="list-style-type: none">7/8 of participants exhibited some improvement in GI symptoms while on the BCP only arm8/8 of participants exhibited some improvement in GI symptoms while on the combination treatment arm↑ percentage of normal stool consistency by the combination treatment ($p = 0.047$)3/7 had increased appetite and consumption of novel foods on the BCP only treatment1/7 had increased appetite and consumption of novel foods on the combination treatment armNo differences in adaptive behaviors were observed based on the ABAS-II questionnaire or repetitive behaviors based on the RBS-RIn the ABC questionnaire: in the BCP only group, there was a significant reduction in irritability ($p = 0.003$), stereotypy ($p = 0.006$), hyperactivity ($p = 0.007$), and total scores ($p = 0.006$), along with a trend toward significant reduction in lethargy ($p = 0.076$).In the ABC questionnaire: The combination treatment demonstrated a significant reduction only in lethargy ($p = 0.0499$).General lack of global changes to the fecal microbiome with either treatmentNo global changes in fecal, urinary or serum metabolite profiles based on treatmentIn stimulated cells, the frequency of CD4+/IL-13 + T cells was significantly lower after combination treatment ($p = 0.006$). There was also a significant reduction in the frequency of CD8+/TNF-α + T cells with the BCP only treatment ($p = 0.024$)	<ul style="list-style-type: none">BCP appears to be well-tolerated in the children as its own treatment as well as when combined with the probiotic<i>Bifidobacterium infantis</i>	<ul style="list-style-type: none">Small sample sizeHigh heterogeneity of symptoms between participantsLarger well-controlled trials are needed to determine the efficacy of these treatments
Liu et al. (2019)	ASD: 71 (36/35)	INT: 10.11 ± 2.34 PL: 9.91 ± 2.33	All boys	<ul style="list-style-type: none">Strain(s): <i>Lactobacillus plantarum</i> P5128Daily amount: 3×10^{10} CFUForm: CapsulesFrequency: once dailyTreatment duration: 4 weeks	<ul style="list-style-type: none">The Clinical Global Impression-Severity (CGI-S)The Clinical Global Impression-Improvement (CGI-I)ADI-R, ABC-T, CBCL, SRS, and SNAP-IV-T questionnaires	<ul style="list-style-type: none">No statistically significant differences in behavioral scores were detected between probiotics and placebo control groupsPost hoc subgroup analysis showed a small but statistically significant improvement in SNAP-IV-T total score ($p = 0.02$) and opposition/defiance subscale score ($p = 0.03$) in probiotics groups	<ul style="list-style-type: none"><i>Lactobacillus plantarum</i> P5128 can ameliorate some autism symptoms, primarily those associated with disruptive and rule-breaking behaviors and hyperactivity/impulsivityThe efficacy of Probiotic intervention seemed to be age-dependent, with better effects noticed on younger children than older children	<ul style="list-style-type: none">The duration of the intervention was limitedIt did not evaluate prolonged outcomes including the continuation of benefits and/or possible recurrences of disorders upon the termination of consumptionAll subjects were allowed to keep their original medication and maintain all their therapies

(Continues)

TABLE 3 (Continued)

Reference	Sample size (INT/PL)	Mean age in years ± SD	Gender (M/F)	Study compound (way of administration; orally)	Biomarker(s)/outcome measurements	Difference between INT and placebo groups	Association with clinical features	Limitations/Notes
Shaaban et al. (2018)	• ASD: 30 • NC: 30	• ASD: 84.77 ± 16.37 months (5–9 years) • NC: age-matched with ASD PTs	• ASD: (19/11)	• Strain(s): <i>Lactobacillus acidophilus</i> , <i>Lactobacillus rhamnosus</i> , and <i>Bifidobacteria longum</i> • Daily amount: 100 × 10 ⁶ CFU • Form: Powder • Frequency: once daily • Treatment duration: 3 months	• Stool quantitative real-time PCR • Autism Treatment Evaluation Checklist (ATEC) • The Gastrointestinal Severity Index • (6-GSI)	• Significant increases in the levels of both <i>Bifidobacterium</i> and <i>Lactobacillus</i> in stool PCR of the autistic children (<i>p</i> < 0.0001) • The total ATEC scores were significantly decreased following probiotic supplementation among autistic children, indicating a decrease in the severity of ASD symptoms (<i>p</i> = 0.0001) • Significant improvement observed in the total 6-GSI score (<i>p</i> < 0.0001) with significant reduction in the scores of constipation (<i>p</i> < 0.01), stool consistency (<i>p</i> < 0.023), flatulence (<i>p</i> < 0.037), and abdominal pain (<i>p</i> < 0.002) following probiotic supplementation	• Probiotics have beneficial effects on both behavioral and GI manifestations of ASD as an adjuvant therapy	• Single-center study with a small number of patients • Lack of a placebo control group • The autistic cohort received behavioral therapy during the probiotic administration • A great deal of additional wide-scale randomized controlled trials are needed
Grossi et al. (2016)	ASD: 1(1 INT)	12	Male	• Strain(s) and daily amount: 9 × 10 ¹⁰ CFU <i>Bifidobacterial</i> , 8 × 10 ¹⁰ CFU <i>lactobacilli</i> , 2 × 10 ¹⁰ CFU <i>Streptococci</i> • Form: Powder • Frequency: NA • Treatment duration: 4 weeks	Diagnosis of ASD according to DSM-V criteria was confirmed by ADOS-2 assessment (Autism Diagnostic Observation Schedule).	• Reduced the severity of abdominal symptoms • Improvement in Autistic core symptoms • Social Affect domain score of ADOS decreased from 20 to 17	• Appropriate use of probiotics may help to fight against ASD by lowering both the ASD and GI symptoms	Single case study
Tomova et al. (2015)	• ASD: 10 • Siblings: 9 • NC: 10	• ASD: (2–9) • Siblings: (5–17) • NC: (2–11)	• ASD: (9/1) • Siblings: (7/2) • NC: 10 boys	• Strain(s): 3 strains of <i>Lactobacillus</i> , 2 strains of <i>Bifidobacteri</i> a and one strain of <i>Streptococcus</i> • Daily amount: NA • Form: Capsules • Frequency: three times daily • Treatment duration: 4 months	• Cytokine TNFα measurement in the stool • Stool microbiome analysis (real-time PCR)	• ↑ Fecal TNFα in the PTs compared to NCs and PTs after probiotic implementation. • A strong correlation between TNFα levels and GI symptoms • Probiotic supplementation normalized Bacteroidetes/Firmicutes ratio, Desulfovibrio spp. and Bifidobacterium spp • No correlation between plasma levels of oxytocin, testosterone, DHEA-S, and fecal microbiota	• Appropriate use of probiotics may help to fight against ASD by lowering both the ASD and GI symptoms	• Small sample size
West Md and Roberts (2013)	ASD: 35 (all INT)	ASD: (3–16)	NA	• Strain(s) and daily amount: <i>Delpro</i> ® (<i>Lactococcus acidophilus</i> , <i>Lactobacillus casei</i> , <i>Lactobacillus delbruecki</i> , <i>Bifidobacteria longum</i> , <i>Bifidobacteria bifidum</i> ; 2 billion CFU each) + 8 mg of Del-immune V® • Form: capsules and powder consecutively • Frequency: 3 times daily • Treatment duration: 21 days	• Autism Treatment Evaluation Checklist (ATEC) • 21-day stool frequency	• 48% reported decreases in diarrhea severity and 52% reported decreases in constipation severity • 88% reported decreases in total ATEC score with significant improvements in all ATEC domains • Increase in stool frequency	• Probiotic/immunomodulator Delpro® may have a significant benefit in the treatment of GI distress and other ATEC signs and symptoms among this population	• No standardization of stool consistency • No control arm of no-treatment or PL volunteered for this study, which may have introduced a selection bias • Small sample size • Lack of regularly scheduled ATEC assessments limits the interpretation of these results • Variation in respondent diet was not assessed. • Short-term intervention

(Continues)

TABLE 3 (Continued)

Reference	Sample size (INT/PL)	Mean age in years ± SD	Gender (M/F)	Study compound (way of administration: orally)	Biomarker(s)/outcome measurements	Difference between INT and placebo groups	Association with clinical features	Limitations/Notes
Kaluzna-Czaplinska and Blaszczyk (2012)	ASD: 22 (all INT)	ASD: 5.6 ± 1.6	INT: (20/2)	<ul style="list-style-type: none">Strain(s): <i>Lactobacillus acidophilus</i> (strain Rosell-11)Daily amount: 5 × 10⁹ CFU/gForm: CapsuleFrequency: twice dailyTreatment duration: 2 months	<ul style="list-style-type: none">D-arabinitol (DA) and L-arabinitol (LA) were identified by capillary GC/MSGI problems, dietary characteristics, and AB use were collected for the study group from individual questionnaires	<ul style="list-style-type: none">* Significant improvement in very important behaviors as the ability of concentration and carrying out the order	<ul style="list-style-type: none">Probiotic supplementation led to a significant decrease in DA and DA/LA ratio and to a significant improvement in the ability of concentration and carrying out orders	<ul style="list-style-type: none">Small sample size
Adams et al. (2011)	ASD: 58 NC: 39	ASD: 6.91 ± 3.4 NC: 7.7 ± 4.4	PTs: (50/8) NC: (18/21)	<ul style="list-style-type: none">Strain(s): NADaily amount: NAForm: NAFrequency: NATreatment duration: NA	<ul style="list-style-type: none">GI symptoms (assessed by the 6-GSI)The severity of autism (assessed by the ATEC)	<ul style="list-style-type: none">Probiotics did not have a significant effect on most of the beneficial bacteriaThe probiotic group had a lower level of lysozyme than the A-No-Probiotic group	<ul style="list-style-type: none">GI problems are associated with autism severityIt is possible that probiotics decrease the need for lysozyme to be excreted to defend against the pathogenic bacteria	<ul style="list-style-type: none">No additional verification of the diagnosis after starting the studyComplicated study analysis
Parracho et al. (2010)	ASD: 22 (11/11)	(4–16)	(20/2)	<ul style="list-style-type: none">Strain(s): <i>Lactobacillus plantarum</i> WCFS1Daily amount: 4.5 × 10¹⁰ CFUForm: CapsulesFrequency: NATreatment duration: 3 weeks	<ul style="list-style-type: none">Bacterial population levels were examined using fluorescence in situ hybridization (FISH).GI function and symptoms diaries were filled by parents.	<ul style="list-style-type: none">Probiotics significantly increased the numbers of <i>Lactobacilli/enterococci</i> in the fecal microbiota of ASD childrenProbiotic feeding also resulted in significant differences in the stool consistency compared to placeboBehavior scores: an overall indicator of behavioral/emotional disturbances (TBPS) was not significantly different between the two groups	<ul style="list-style-type: none">There is a potential benefit of <i>Lactobacillus plantarum</i> WCFS1 probiotic feeding in ASD PTs	<ul style="list-style-type: none">The extremely high dropout rateRelatively high inter-individual variabilityShort-term probiotic intervention
Partty et al. (2015)	ADHD: 75 (40/35)	INT and PL groups were included during the first 6 months of life then they were followed-up to 13 years	INT: (24/16) PL: (16/19)	<ul style="list-style-type: none">Strain(s): <i>Lactobacillus rhamnosus</i> GG (ATCC 53103)Daily amount: 10¹⁰ CFUForm: CapsulesFrequency: once dailyTreatment duration: 6 months	<ul style="list-style-type: none">ICD-10 diagnostic criteria for diagnosing ADHD and Asperger syndromeGut microbiota was assessed using fluorescein in situ hybridization (FISH) and qPCR, and indirectly by determining the blood group secretor type	<ul style="list-style-type: none">ADHD or Asperger syndrome was diagnosed in 6/35 children in the PL and none in the probiotic group<i>Bifidobacterium</i> species bacteria in feces during the first 6 months of life was lower in the affected children	<ul style="list-style-type: none">Probiotic supplementation early in life may reduce the risk of neuropsychiatric disorder development	<ul style="list-style-type: none">The study was originally designed and statistically powered for the prevention of atopic eczema, not for the prevention of ADHD and ASDDropouts were quite considerable during the follow-up

(Continues)

TABLE 3 (Continued)

Reference	Sample size (INT/PL)	Mean age in years ± SD	Gender (M/F)	Study compound (way of administration: orally)	Biomarker(s)/outcome measurements	Difference between INT and placebo groups	Association with clinical features	Limitations/Notes
Harding et al. (2003)	ADHD: 20 (10 INT, 10 Ritalin)	• INT: (7–12) • Ritalin: (7–12)	• INT: NA • Ritalin: NA	• A mix of vitamins, minerals, phytonutrients, amino acids, essential fatty acids, phospholipids, and probiotics was used • Strain(s): <i>Lactobacillus acidophilus</i> and <i>Bifidus</i> • The daily amount, form, frequency, and treatment duration were determined by neuropsychiatric nurse clinical specialist	• Intermediate Visual and Auditory/Continuous Performance Test (IVA/CPT) • DSM-IV diagnostic criteria • The Conner's Parent Rating Scale	• INT and Ritalin groups showed significant gains ($p \leq 0.01$) on the IVA/CPT's Full Scale Response Control.	• Synergistic combinations of dietary supplements directed at the more probable underlying etiologies of ADHD were equivalent to Ritalin treatment as measured by improvements in attention and self-control using IVA/CPT testing.	• Small sample size
Ghaderi et al. (2019)	SZ (30/30)	• INT: 44.8 ± 8.3 • PL: 43.2 ± 6.0	• INT (28/2) • PL: (28/2)	• Strain(s): 50,000 IU of vitamin D3 every 2 weeks plus 8×10^9 CFU/day of probiotic supplements containing <i>Lactobacillus acidophilus</i> , <i>Bifidobacterium bifidum</i> , <i>Lactobacillus reuteri</i> , and <i>Lactobacillus fermentum</i> (each 2×10^9 CFU) Treatment duration: 12 weeks	• Positive and Negative Syndrome Scale (PANSS) • The Brief Psychiatric Rating Scale (BPRS) • Total antioxidant capacity • Total glutathione (GSH) and malondialdehyde concentrations • Nitric oxide levels • Serum insulin concentrations • Fasting plasma glucose • The homeostasis model of assessment-insulin resistance (HOMA-IR) • The quantitative insulin sensitivity check index (QUICKI)	• ↑ General PANSS ($p = 0.004$) • ↑ Total PANSS ($p = 0.01$) • ↑ Anti-oxidant capacity ($p = 0.007$) • ↓ malondialdehyde ($p = 0.01$) • ↓ high sensitivity C-reactive protein ($p = 0.001$) • ↓ fasting plasma glucose ($p = 0.01$) • ↓ insulin concentrations ($p < 0.001$) • ↓ homeostasis model of assessment-estimated insulin resistance ($p < 0.001$) • ↓ triglycerides ($p = 0.01$) • ↓ total cholesterol ($p = 0.04$) • ↓ total-/HDL-cholesterol ratio ($p = 0.04$)	• Probiotic and vitamin D for 12 weeks to chronic schizophrenia had beneficial effects on the general and total PANSS score and metabolic profiles.	• All patients were hospitalized during the intervention

Okubo et al. (2018)	SZ: 29	INT: 45 ± 16	INT: (11/17)	• Strain(s): <i>Bifidobacterium breve</i> A-1 • Daily amount: 10^{11} CFU • Form: Sachet • Frequency: Twice daily (with food) • Treatment duration: 4 weeks	• Hospital Anxiety and Depression Scale (HADS) • Positive and Negative Syndrome Scale (PANSS) • Blood test • Fecal microbiome	• HADS ($p = 0.037$) • PANSS ($p = 0.004$)	• Probiotic supplementation may reduce the severity of anxiety and depressive symptoms in SZ by enhancing the gut epithelial barrier function	• Short treatment duration • Open-label, single-arm study
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(Continues)

TABLE 3 (Continued)

Reference	Sample size (INT/PL)	Mean age in years ± SD	Gender (M/F)	Study compound (way of administration: orally)	Biomarker(s)/outcome measurements	Difference between INT and placebo groups	Association with clinical features	Limitations/Notes
Severance et al. (2017)	SZ: 56 (30/27)	• INT: 44.7 ± 11.4 • PL: 48.11 ± 9.6	• INT: (22/8) • PL: (15/11)	• Strain(s): <i>Lactobacillus rhamnosus</i> strain GG, <i>Bifidobacterium animalis</i> subs. <i>Lactis</i> strain Bb12 • Daily amount: 10 ⁹ CFU (per organism) • Form: Tablet • Frequency: Once daily (with food) • Treatment duration: 14 weeks	• Levels of antibodies to <i>C. albicans</i> and <i>S. cerevisiae</i> • Positive and Negative Syndrome Scale (PANSS) • Query gastrointestinal functioning	• <i>C. albicans</i> IgG level in males (<i>p</i> < 0.001) • PANSS in seronegative <i>C. albicans</i> males (<i>p</i> < 0.06)	• Probiotic supplementation may lead to an improvement in bowel functions due to the correction of yeast overgrowth	• Interpretation of study results is limited by the exploratory nature and small sample sizes
Tomasik et al. (2015)	SZ: 57 (30/27)	• INT: 44.8 ± 11.2 • PL: 48.1 ± 9.2	• INT: 22/9 • PL: 16/11	• Strain(s): <i>Lactobacillus rhamnosus</i> strain GG, <i>Bifidobacterium animalis</i> subs. <i>Lactis</i> strain Bb12 • Daily amount: 10 ⁹ CFU (per organism) • Form: Tablet • Frequency: Once daily (with food) • Treatment duration: 14 weeks	• 47 immune-related serum proteins • Von Willebrand Factor (<i>p</i> = 0.047) Monocyte Chemotactic Protein 1 (<i>p</i> = 0.054) • Brain-derived Neurotrophic Factor (<i>p</i> = 0.063) • RANTES (<i>p</i> = 0.069) • Macrophage Inflammatory Protein 1 beta (<i>p</i> = 0.080)	• Probiotic supplementation may improve gastrointestinal leakage control in SZ.	• Probiotic supplementation may lead to an improvement in bowel functions due to the correction of yeast overgrowth	• Open-label, single-arm study • Not able to detect all targeted cytokines in clinical samples • Investigated patients with SZ on stable, long- term antipsychotics, but immune modularly effect still possible • A small number of immune-related serum proteins was identified as significantly or borderline different between the two groups
Dickerson et al. (2014)	SZ: 65 (33/32)	• INT: 44.4 ± 11.0 • PL: 48.1 ± 9.4	• INT: (23/47) • PL: (19/40)	• Strain(s): <i>Lactobacillus rhamnosus</i> strain GG, <i>Bifidobacterium animalis</i> subs. <i>Lactis</i> strain Bb12 • Daily amount: 10 ⁹ CFU (per organism) • Form: Tablet • Frequency: Once daily (with food) • Treatment duration: 14 weeks	• Positive and Negative Syndrome Scale (PANSS) • Query gastrointestinal functioning	• PANSS (<i>p</i> = 0.25) • Gastrointestinal functioning (<i>p</i> = 0.003)	• Probiotic supplementation may make patients with SZ less likely to develop severe bowel difficulties.	• Not a detailed measurement of gastrointestinal functioning • No complete history of participants' gastrointestinal symptoms and associated symptoms
Dickerson et al. (2018)	BD: 66 (33/33)	• INT: 37.9 ± 11.7 • PL: 33.3 ± 13.3	• INT: 9/24 • PL: 15/18	• Strain(s): <i>Lactobacillus rhamnosus</i> strain GG, <i>Bifidobacterium animalis</i> subs. <i>Lactis</i> strain Bb12 • Daily amount: > 10 ⁸ CFU • Form: Tablet • Frequency: Once daily (with food) • Treatment duration: 24 weeks	• Time to neuropsychiatric inpatient rehospitalization • The Brief Neuropsychiatric Rating Scale (BNRS) • Symptom assessment (YMRS) • Montgomery- Åsberg Depression Rating Scale (MADRAS)	• Time to neuropsychiatric inpatient rehospitalization (<i>p</i> = 0.017) • BNRS (<i>p</i> < 0.0001) • YMRS (<i>p</i> < 0.0001)	• Probiotic supplementation may alter clinical course following mania and lessen neuropsychiatric symptom severity in BD mania.	• Treatment received after hospital discharge was not standardized. • The sample may not have fully representative of patients hospitalized for mania. • The effect of probiotics on gut microbiome/ inflammation in CNS was not directly measured

(Continues)

TABLE 3 (Continued)

Reference	Sample size (INT/PL)	Mean age in years ± SD	Gender (M/F)	Study compound (way of administration: orally)	Biomarker(s)/outcome measurements	Difference between INT and placebo groups	Association with clinical features	Limitations/Notes
Reininghaus et al. (2018)	BD: 20 (all INT)	INT: 51.5 ± 11.5	INT: 11/9	<ul style="list-style-type: none">Strain(s): <i>Lactobacillus casei</i> W56, <i>Lactobacillus acidophilus</i> W22, <i>Lactobacillus paracasei</i> W20, <i>Bifidobacterium lactis</i> W51, <i>Lactobacillus salivarius</i> W24, <i>Lactococcus lactis</i> W19, <i>Bifidobacterium lactis</i> W52, <i>Lactobacillus Plantarum</i> W62, <i>Bifidobacterium bifidum</i> W23Daily amount: 2.25×10^{10} CFUForm: SachetFrequency: Once daily (empty stomach)Treatment duration: 12 weeks	<ul style="list-style-type: none">Trial Masking Test A (TMT-A)Digit symbol testTrial Masking Test B (TMT-B)Digit-span-testMittenecker Pointing Test	<ul style="list-style-type: none">Digit symbol test ($p < 0.001$)TMT-B ($p < 0.05$)	<ul style="list-style-type: none">Probiotic supplementation may increase cognitive function in patients with BD	<ul style="list-style-type: none">Open-label, single-arm studySmall sample sizeSmall cognitive test batteryMedications/Lifestyle changes were not taken into consideration

Note: Publications are arranged in a reversed chronological order (from newest to oldest) per diagnosis.

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; INT, intervention; NA, not available; NC, non-neuropsychiatric comparison subject; PL, placebo; PT, patient; SZ, schizophrenia.

size, decreased process length, and increased major projection along with increased activated microglia, leading to synaptic stripping, impaired hippocampal plasticity, decreased dendritic spine density, as well as decreased synaptic protein such as postsynaptic density protein 95, synaptophysin, and spinophilin along with cognitive impairment (Bocarsly et al., 2015; Chunchai et al., 2018; Hao, Dey, Yu, & Stranahan, 2016). The morphological abnormalities in microglia caused by high-fat diet consumption were rescued by probiotic and prebiotic supplementation concurrent with amelioration in microglial activation and cognitive function (Chunchai et al., 2018).

In summary, changing the composition of the intestinal microbiota *via* diet, probiotics, prebiotics, and FMT showed a trend in improving the psychiatric conditions and/or their concurrent GI complaints. To this end, we hypothesize that the effectiveness of these dietary and probiotic interventions in improving symptoms in the aforementioned studies can at least partly be explained *via* interaction with microglia function and perhaps modifying synaptic pruning and neuronal connections, leading to a change in synaptic density. Moreover, most of the studies using these interventions have not resulted in adverse events besides incidental bloating sensations and changes in stool consistency, and thus contribute to compliance (Allen, Martinez, Gregorio, & Dans, 2010; Huurre, Laitinen, Rautava, Korkeamäki, & Isolauri, 2008; Kuitunen et al., 2009; Kukkonen et al., 2008; Luoto, Laitinen, Nermes, & Isolauri, 2010; Niers et al., 2009). For these reasons, these interventions could form a beneficial supportive treatment in neuropsychiatric disorders.

7 | CONCLUSION

Different patterns of synaptic pruning in neuropsychiatric disorders may suggest a common pathogenic pathway (de Silva, 2018). Modification of synaptic pruning can be a promising target for treating or preventing these neuropsychiatric symptoms. As the intestinal microbiota may have an influence on synaptic pruning *via* regulation of microglial activation, the optimization of the microbiota composition might be an easy way to modify the disturbed synaptic pruning in neuropsychiatric disorders during specific developmental stages, which, in turn, can alleviate some symptoms (Figure 2). As the second decade in life is the most prominent period for synaptic pruning, therapeutic interventions to improve intestinal microbiota would be the best provided to people with a high risk of SZ and BD during that period, even before the diagnosis is made or to already diagnosed patients with ASD. Possible ways to improve or re-establish healthy microbiota are through dietary interventions, administration of probiotics/prebiotics or fecal transplants. To this end, we recommend such interventions to be used as a supportive therapeutic approach in neuropsychiatric patients or in individuals with high genetic risk of developing a neuropsychiatric disorder. As the effects of these interventions can be time-sensitive, the critical time window for having good effects in the aforementioned neuropsychiatric disorders should be investigated in more detail. The effect of these

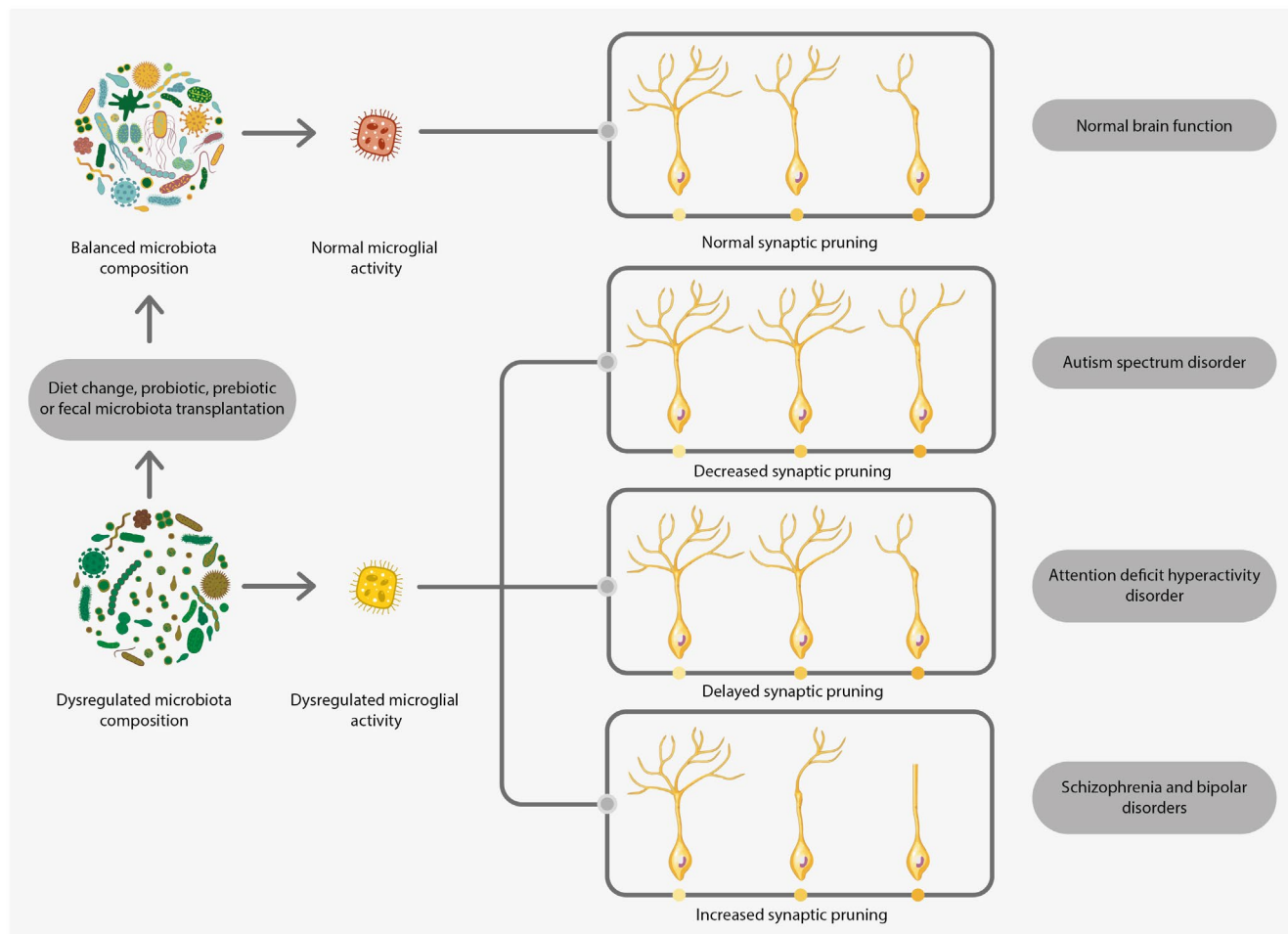


FIGURE 2 Hypothesis model of the effect of the intestinal microbiota modulation on alleviating neuropsychiatric symptoms. The dysregulation of intestinal microbiota is associated with a dysregulation in microglial activity, causing an imbalance in the synaptic pruning process. Different patterns of dysregulated synaptic pruning have been linked to various neuropsychiatric phenotypes including autism spectrum disorder, attention deficit hyperactivity disorder, schizophrenia, and bipolar disorder. The modulation of the intestinal microbiota via diet change, probiotic, prebiotic, and fecal microbiota transplantation might balance the microglial activity and synaptic pruning, leading to normal brain function and alleviation of neuropsychiatric symptoms [Color figure can be viewed at wileyonlinelibrary.com]

therapeutic interventions on the cortical thickness, as an indicator of synaptic pruning, should be tested by means of MRI. Moreover, the microglial activation and microglial gene expression assessed in cerebrospinal fluid may be used as markers for testing the efficacy of probiotic and prebiotic administration in different neuropsychiatric disorders and for determining the optimum duration of treatment.

KEY POINTS

- Normal brain function is associated with an initial formation of excessive synapses that have to be removed in a controlled and timely manner in a process called synaptic pruning.
 - Various patterns of synaptic pruning dysregulation play an important role in the development of different neuropsychiatric disorders.
 - The intestinal microbiota may affect synaptic pruning through microglial activation.

- Current clinical research on using probiotic and prebiotic supplementations in addition to changing the diet and fecal microbiota transplantation demonstrate biological and clinical efficacy in ASD, ADHD, SZ, and BD, which might be partly explained by a modification of synaptic pruning.

DECLARATION OF TRANSPARENCY

The authors, reviewers, and editors affirm that in accordance with the policies set by the *Journal of Neuroscience Research*, this manuscript presents an accurate and transparent account of the study being reported and that all critical details describing the methods and results are present.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, A.E.; Writing – Original Draft, A.E.; Methodology, I.E.J. and M.G.; Writing – Review & Editing, B.C.M.H. and I.E.C.S.

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